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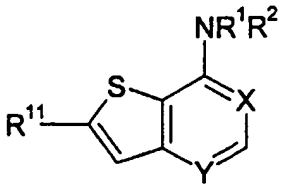
R11 = Lthroughout

(54) Title: THIOPHENE DERIVATIVES USEFUL AS ANTICANCER AGENTS



(1)

(57) Abstract: The invention relates to compounds of the formula (1) or a pharmaceutically acceptable salt and to pharmaceutically acceptable salts and hydrates thereof, wherein X, Y, R^1, R^2 and R^{11} are as defined herein. The invention also relates to pharmaceutical compositions containing the compounds of formula (1) and to methods of treating hyperproliferative disorders in a mammal by administering the compounds of formula (1).

Y = N
X = C-CN

R1 = H
R2 = heterocyclic
R11 = mostly CONRR

THIOPHENE DERIVATIVES USEFUL AS ANTICANCER AGENTS

Background of the Invention

This invention relates to novel thiophene derivatives that are useful in the treatment of hyperproliferative diseases, such as cancers, in mammals. This invention also relates to a method of using such compounds in the treatment of hyperproliferative diseases in mammals, especially humans, and to pharmaceutical compositions containing such compounds.

Compounds that are useful in the treatment of hyperproliferative diseases are referred to the following patent applications: PCT international patent application number PCT/IB97/00675 (filed June 11, 1997), United States provisional patent application number 60/041846 (filed April 9, 1997), United States provisional patent application number 60/031862 (filed November 27, 1996), United States provisional patent application number 60/028881 (filed October 17, 1996), PCT international patent application number PCT/IB97/00584 (filed May 22, 1997), United States patent application number 08/653,786 (filed May 28, 1996), PCT international patent application publication number WO 96/40142 (published December 19, 1996), PCT international patent application publication number WO 97/13771 (published April 17, 1997), PCT international patent application publication number WO 95/23141 (published August 31, 1995) and United States patent application having attorney reference number PC9882B (filed February 10, 2000). Each of the foregoing United States and PCT international patent applications is incorporated herein by reference in its entirety.

It is known that a cell may become cancerous by virtue of the transformation of a portion of its DNA into an oncogene (i.e. a gene that upon activation leads to the formation of malignant tumor cells). Many oncogenes encode proteins which are aberrant tyrosine kinases capable of causing cell transformation. Alternatively, the overexpression of a normal proto-oncogenic tyrosine kinase may also result in proliferative disorders, sometimes resulting in a malignant phenotype.

Receptor tyrosine kinases are large enzymes that span the cell membrane and possess an extracellular binding domain for growth factors such as epidermal growth factor, a transmembrane domain, and an intracellular portion that functions as a kinase to phosphorylate specific tyrosine residue in proteins and hence to influence cell proliferation. The foregoing tyrosine kinases may be classified as growth factor receptor (e.g. EGFR, PDGFR, FGFR and erbB2) or non-receptor (e.g. c-src and bcr-abl) kinases. It is known that such kinases are often aberrantly expressed in common human cancers such as breast cancer, gastrointestinal cancer such as colon, rectal or stomach cancer, leukemia, and ovarian, bronchial or pancreatic cancer. Aberrant erbB2 activity has been implicated in breast, ovarian, non-small cell lung, pancreatic,gastric and colon cancers. It has also been shown that epidermal growth factor receptor (EGFR) is mutated or overexpressed in many human cancers such as brain, lung,

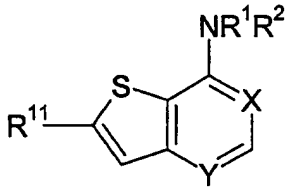
squamous cell, bladder, gastric, breast, head and neck, oesophageal, gynecological and thyroid cancers. Thus, it is believed that inhibitors of receptor tyrosine kinases, such as the compounds of the present invention, are useful as selective inhibitors of the growth of mammalian cancer cells.

It has also been shown that EGFR inhibitors may be useful in the treatment of pancreatitis and kidney disease (such as proliferative glomerulonephritis and diabetes-induced renal disease), and may reduce successful blastocyte implantation and therefore may be useful as a contraceptive. See PCT international application publication number WO 95/19970 (published July 27, 1995).

It is known that polypeptide growth factors such as vascular endothelial growth factor (VEGF) having a high affinity to the human kinase insert-domain-containing receptor (KDR) or the murine fetal liver kinase 1 (FLK-1) receptor have been associated with the proliferation of endothelial cells and more particularly vasculogenesis and angiogenesis. See PCT international application publication number WO 95/21613 (published August 17, 1995). Agents, such as the compounds of the present invention, that are capable of binding to or modulating the KDR/FLK-1 receptor may be used to treat disorders related to vasculogenesis or angiogenesis such as diabetes, diabetic retinopathy, hemangioma, glioma, melanoma, Kaposi's sarcoma and ovarian, breast, lung, pancreatic, prostate, colon and epidermoid cancer.

Summary Of The Invention

The present invention relates to compounds of the formula 1



1

or a pharmaceutically acceptable salt, prodrug or hydrate thereof,

X is N, CH or C(CN);

Y is N, CH, CF, or N→0;

R^1 is H or C_1-C_6 alkyl;

R^2 is 5 to 13 membered heterocyclic, wherein said R^2 group is optionally substituted by 1 to 5 R^5 substituents,

each R^5 is independently selected from halo, cyano, trifluoromethoxy, trifluoromethyl, $-C(O)R^8$, $-NR^6C(O)R^7$, $-C(O)NR^6R^7$, $-NR^6R^7$, $-OR^9$, $-SO_2NR^6R^7$, $-SO_2R^6$, $-NR^6SO_2R^7$, $-NR^6SO_2NR^9R^{10}$, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, $-(CH_2)_jO(CH_2)_qNR^6R^7$,

$-(CH_2)_tO(CH_2)_qOR^9$, $-(CH_2)_tOR^9$, $-S(O)_j(C_1-C_6$ alkyl), $-(CH_2)_t(C_6-C_{10}$ aryl), $-(CH_2)_t$(5 to 10 membered heterocyclic), $-(CH_2)_tO(CH_2)_q$(5 to 10 membered heterocyclic), $-C(O)(CH_2)_t$(5 to 10 membered heterocyclic), $-(CH_2)_jNR^7(CH_2)_qNR^6R^7$, $-(CH_2)_jNR^7CH_2C(O)NR^6R^7$, $-(CH_2)_jNR^7(CH_2)_qNR^9C(O)R^8$, $-(CH_2)_jNR^7(CH_2)_tO(CH_2)_qOR^9$, $-(CH_2)_jNR^7(CH_2)_qS(O)_j(C_1-C_6$ alkyl), $-(CH_2)_jNR^7(CH_2)_tR^6$, $-SO_2(CH_2)_t(C_6-C_{10}$ aryl), and $-SO_2(CH_2)_t$(5 to 10 membered heterocyclic), wherein j is an integer from 0 to 2, t is an integer from 0 to 6, q is an integer from 2 to 6, the $-(CH_2)_q-$ and $-(CH_2)_t-$ moieties of the foregoing R^5 groups optionally include a carbon-carbon double or triple bond where t is an integer from 2 to 6, and the alkyl, aryl and heterocyclic moieties of the foregoing R^5 groups are optionally substituted by 1 to 3 substituents independently selected from halo, cyano, trifluoromethyl, $-C(O)R^8$, $-NR^6C(O)R^7$, $-C(O)NR^6R^7$, $-(CH_2)_tNR^6R^7$, $-SO_2R^6$, $-SO_2NR^6R^7$, C_1-C_6 alkyl, $-(CH_2)_t$(5 to 10 membered heterocyclic), $-(CH_2)_tO(CH_2)_qOR^9$, and $-(CH_2)_tOR^9$, wherein t is an integer from 0 to 6 and q is an integer from 2 to 6;

each R^6 and R^7 is independently selected from H, C_1-C_6 alkyl, $-(CH_2)_t(C_6-C_{10}$ aryl), $-(CH_2)_t$(5 to 10 membered heterocyclic), $-(CH_2)_tO(CH_2)_qOR^9$, and $-(CH_2)_tOR^9$, wherein t is an integer from 0 to 6 and q is an integer from 2 to 6, and the alkyl, aryl and heterocyclic moieties of the foregoing R^6 and R^7 groups are optionally substituted by 1 to 3 substituents independently selected from halo, cyano, trifluoromethyl, $-C(O)R^8$, $-NR^9C(O)R^{10}$, $-C(O)NR^9R^{10}$, $-NR^9R^{10}$, C_1-C_6 alkyl, $-(CH_2)_t(C_6-C_{10}$ aryl), $-(CH_2)_t$(5 to 10 membered heterocyclic), $-(CH_2)_tO(CH_2)_qOR^9$, and $-(CH_2)_tOR^9$, wherein t is an integer from 0 to 6 and q is an integer from 2 to 6, with the proviso that where R^6 and R^7 are both attached to the same nitrogen, then R^6 and R^7 are not both bonded to the nitrogen directly through an oxygen;

each R^8 is independently selected from H, C_1-C_{10} alkyl, $-(CH_2)_t(C_6-C_{10}$ aryl), and $-(CH_2)_t$(5 to 10 membered heterocyclic), wherein t is an integer from 0 to 6;

each R^9 and R^{10} is independently selected from H and C_1-C_8 alkyl;

R^{11} is $-C(O)NR^{12}R^{13}$, $-(CH_2)_tNR^{12}R^{13}$, $-NR^{12}C(=O)R^{13}$, $-SO_2R^{12}$, $-SO_2NR^{12}R^{13}$, $-NR^9SO_2R^{12}$, $-NR^9SO_2NR^{12}R^{13}$, $-C(=N-OR^{12})R^{13}$, $-C(=NR^{12})R^{13}$, $-NR^9C(=NR^{12})R^{13}$, $-C(=NR^{12})NR^9R^{13}$, $-NR^9C(=NR^{12})NR^9R^{13}$, $-C(O)R^{12}$ and $-CO_2R^{12}$ and wherein each R^{12} and R^{13} is independently selected from H, C_1-C_6 alkyl, $-(CH_2)_t(C_3-C_{10}$ cycloalkyl), $-(CH_2)_t(C_6-C_{10}$ aryl), $-(CH_2)_t$(5 to 10 membered heterocyclic), $-(CH_2)_tO(CH_2)_qOR^9$, $-(CH_2)_tOR^9$, wherein t is an integer from 0 to 6 and q is an integer from 2 to 6, and the alkyl, aryl and heterocyclic moieties of the foregoing R^{12} and R^{13} groups are optionally substituted by 1 to 3 substituents independently selected from R^5 or R^{12} and R^{13} taken together with the nitrogen to which they are attached to form a C_5-C_9 azabicyclic, aziridinyl, az tidinyl, pyrrolidinyl, pip ridinyl, piperazinyl, morpholinyl, thiomorpholinyl, isoquinolinyl, or dihydroisoquinolinyl ring, wherein said C_5-C_9 azabicyclic, aziridinyl, azetidinyl, pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl,

thiomorpholinyl, isoquinolinyl, or dihydroisoquinolinyl ring are optionally substituted by 1 to 5 R^5 substituents, with the proviso R^{12} and R^{13} are not both bonded to the nitrogen directly through an oxygen.

More preferred compounds include those of formula 1, wherein X is CH and Y is CH, CF, or N.

Most preferred compounds include those of formula 1, wherein X is CH and Y is N.

Preferred compound include those of formula 1, wherein R^{11} is $-C(O)NR^{12}R^{13}$, $-SO_2R^{12}$, $-SO_2NR^{12}R^{13}$, $-C(=N-OR^{12})R^{13}$, and $-C(=NR^{12})R^{13}$.

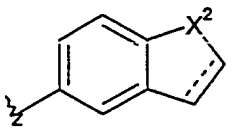
In one preferred embodiment, the compounds of the invention include those of formula 1 wherein R^{11} is $-C(O)NR^{12}R^{13}$, wherein each R^{12} and R^{13} is independently selected from H, C_1-C_6 alkyl, $-(CH_2)_tOR^9$, wherein t is an integer from 0 to 6, and the alkyl moiety of the foregoing R^{12} and R^{13} groups is optionally substituted by 1 to 3 substituents independently selected from halo, cyano, trifluoromethyl, $-C(O)R^8$, $-NR^9C(O)R^{10}$, $-C(O)NR^9R^{10}$, $-NR^9R^{10}$, C_1-C_6 alkyl, $-(CH_2)_t(C_6$-C_{10} aryl), $-(CH_2)_t$(5 to 10 membered heterocyclic), $-(CH_2)_tO(CH_2)_qOR^9$, and $-(CH_2)_tOR^9$, wherein t is an integer from 0 to 6 and q is an integer from 2 to 6, or R^{12} and R^{13} taken together with the nitrogen to which they are attached to form a C_5-C_9 azabicyclic, aziridinyl, azetidinyl, pyrrolidinyl, piperidinyl, piperazinyl, or morpholinyl ring wherein said C_5-C_9 azabicyclic, aziridinyl, azetidinyl, pyrrolidinyl, piperidinyl, piperazinyl, or morpholinyl ring are optionally substituted by 1 to 5 R^5 substituents, with the proviso R^{12} and R^{13} are not both bonded to the nitrogen directly through an oxygen.

In another preferred embodiment, the compounds of the invention include those of formula 1 wherein R^{11} is $-C(O)NR^{12}R^{13}$ wherein R^{12} and R^{13} taken together with the nitrogen to which they are attached form a C_5-C_9 azabicyclic, aziridinyl, azetidinyl, pyrrolidinyl, piperidinyl, piperazinyl, or morpholinyl ring wherein said C_5-C_9 azabicyclic, aziridinyl, azetidinyl, pyrrolidinyl, piperidinyl, piperazinyl, or morpholinyl ring are optionally substituted by 1 to 5 R^5 substituents.

More preferred compounds of formula 1 include those wherein R^{11} is $-C(O)NR^{12}R^{13}$ wherein R^{12} and R^{13} taken together with the nitrogen to which they are attached form a C_5-C_9 azabicyclic, aziridinyl, azetidinyl, or pyrrolidinyl ring wherein said C_5-C_9 azabicyclic, aziridinyl, azetidinyl, or pyrrolidinyl ring are optionally substituted by 1 to 5 R^5 substituents.

Most preferred compounds of formula 1 include those wherein R^{11} is $-C(O)NR^{12}R^{13}$ wherein R^{12} and R^{13} taken together with the nitrogen to which they are attached form a C_5-C_9 azabicyclic, azetidinyl or pyrrolidinyl ring wherein said C_5-C_9 azabicyclic, azetidinyl or pyrrolidinyl ring is optionally substituted by 1 to 5 R^5 substituents.

Other preferred compounds include those of formula 1 wherein R^2 is a group of the formula



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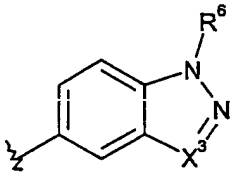

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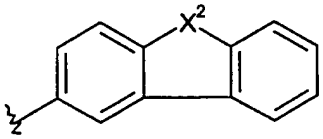

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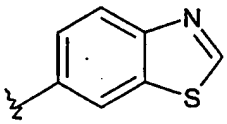

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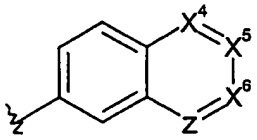
or



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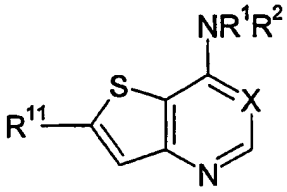
wherein X^2 is -S-, -N(R^6)- or O, and X^3, X^4, X^5, X^6, and Z is N or CH, the dashed line in formula **2** represents an optional double bond, and the above R^2 groups of formulas **2, 4** and **6** are optionally substituted by 1 to 5 R^5 substituents and the R^2 groups of formulas **3** and **5** are optionally substituted by 1 to 3 R^5 substituents.

One embodiment of the invention is directed to compounds of formula 1,



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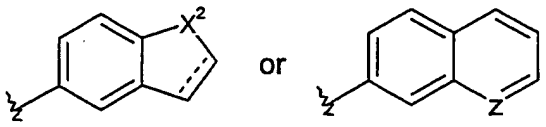
or a pharmaceutically acceptable salt, prodrug or hydrate thereof, wherein X, R^1, R^2, R^5, R^6, R^7, R^8, R^9, R^{10}, R^{11}, R^{12}, and R^{13} are as defined above.

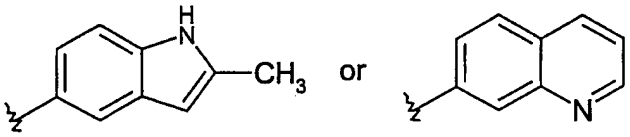
One preferred embodiment of the invention is directed to compounds of formula 1, wherein X is CH; Y is N; R^1 is H; R^2 is



2 6

X^2 is -N(R^6)-, the dashed line in formula **2** represents an optional double bond, Z is CH or N and the above R^2 group of formulas **2** and **6** are optionally substituted by 1 to 5 R^5 and wherein R^5, R^6, R^7, R^8, R^9, R^{10}, R^{11}, R^{12}, and R^{13} are as defined above.

The invention also relates to compounds of formula 1, wherein X is CH; Y is N; R^1 is H; R^2 is



wherein R^5, R^6, R^7, R^8, R^9, R^{10}, R^{11}, R^{12}, and R^{13} are as defined above.

Specifically preferred compounds include those wherein R^2 group is a group of formula **2** or **6**, wherein said formulas **2** and **6** are optionally substituted by 1 to 5 R^5 substituents.

The following are specific compounds of the present invention:

7-(2-Methyl-1H-indol-5-ylamino)-thieno[3,2-b]pyridine-2-carboxylic acid methyl-pyridin-3-ylmethyl-amide;

Azetidin-1-yl-[7-(2-methyl-1H-indol-5-ylamino)-thieno[3,2-b]pyridin-2-yl]-methanone;

[7-(2-Methyl-1H-indol-5-ylamino)-thieno[3,2-b]pyridin-2-yl]-pyrrolidin-1-yl-methanone;

7-(2-Methyl-1H-indol-5-ylamino)-thieno[3,2-b]pyridine-2-carboxylic acid cyclohexyl-methyl-amide;

(2-Methoxymethyl-pyrrolidin-1-yl)-[7-(2-methyl-1H-indol-5-ylamino)-thieno[3,2-b]pyridin-2-yl]-methanone;

7-(2-Methyl-1H-indol-5-ylamino)-thieno[3,2-b]pyridine-2-carboxylic acid methyl-(2-morpholin-4-yl-ethyl)-amide;

N-{1-[7-(2-Methyl-1H-indol-5-ylamino)-thieno[3,2-b]pyridine-2-carbonyl]-pyrrolidin-3-yl}-acetamide;

N-Ethyl-N-{1-[7-(2-methyl-1H-indol-5-ylamino)-thieno[3,2-b]pyridine-2-carbonyl]-pyrrolidin-3-yl}-acetamide;

(3-Methylamino-pyrrolidin-1-yl)-[7-(2-methyl-1H-indol-5-ylamino)-thieno[3,2-b]pyridin-2-yl]-methanone;

(3-Dimethylamino-pyrrolidin-1-yl)-[7-(2-methyl-1H-indol-5-ylamino)-thieno[3,2-b]pyridin-2-yl]-methanone;

(6-Amino-3-aza-bicyclo[3.1.0]hex-3-yl)-[7-(2-methyl-1H-indol-5-ylamino)-thieno[3,2-b]pyridin-2-yl]-methanone;

(3-Dimethylamino-pyrrolidin-1-yl)-[7-(2-methyl-1H-indol-5-ylamino)-thieno[3,2-b]pyridin-2-yl]-methanone;

(2-Methoxymethyl-pyrrolidin-1-yl)-[7-(2-methyl-1H-indol-5-ylamino)-thieno[3,2-b]pyridin-2-yl]-methanone;

(3-Hydroxy-pyrrolidin-1-yl)-[7-(2-methyl-1H-indol-5-ylamino)-thieno[3,2-b]pyridin-2-yl]-methanone;

(2-Hydroxymethyl-pyrrolidin-1-yl)-[7-(2-methyl-1H-indol-5-ylamino)-thieno[3,2-b]pyridin-2-yl]-methanone;

(3-Methoxy-pyrrolidin-1-yl)-[7-(2-methyl-1H-indol-5-ylamino)-thieno[3,2-b]pyridin-2-yl]-methanone;

(3-Ethoxy-azetidin-1-yl)-[7-(2-methyl-1H-indol-5-ylamino)-thieno[3,2-b]pyridin-2-yl]-methanone;

N-Methyl-N-{1-[7-(2-methyl-1H-indol-5-ylamino)-thieno[3,2-b]pyridine-2-carbonyl]-pyrrolidin-3-yl}-acetamide;

cyclobutanecarboxylic acid {1-[7-(2-methyl-1H-indol-5-ylamino)-thieno[3,2-b]pyridine-2-carbonyl]-pyrrolidin-3-yl}-amide; pharmaceutically acceptable salts of said compounds; solvates of said compounds; and prodrugs of said compounds.

The following are specific preferred compounds of the present invention:

(2S)-(2-Methoxymethyl-pyrrolidin-1-yl)-[7-(2-methyl-1H-indol-5-ylamino)-thieno[3,2-b]pyridin-2-yl]-methanone

(+/-)-N-Ethyl-N-{1-[7-(2-methyl-1H-indol-5-ylamino)-thieno[3,2-b]pyridine-2-carbonyl]-pyrrolidin-3-yl}-acetamide

(3S)-(3-Dimethylamino-pyrrolidin-1-yl)-[7-(2-methyl-1H-indol-5-ylamino)-thieno[3,2-b]pyridin-2-yl]-methanone

(+/-)-N-Methyl-N-{1-[7-(2-methyl-1H-indol-5-ylamino)-thieno[3,2-b]pyridine-2-carbonyl]-pyrrolidin-3-yl}-acetamide

(2R)-(2-Methoxymethyl-pyrrolidin-1-yl)-[7-(2-methyl-1H-indol-5-ylamino)-thieno[3,2-b]pyridin-2-yl]-methanone

(3S)-(3-Hydroxy-pyrrolidin-1-yl)-[7-(2-methyl-1H-indol-5-ylamino)-thieno[3,2-b]pyridin-2-yl]-methanone

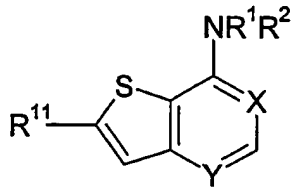
(3R)-(3-Hydroxy-pyrrolidin-1-yl)-[7-(2-methyl-1H-indol-5-ylamino)-thieno[3,2-b]pyridin-2-yl]-methanone

(+/-)-Cyclobutanecarboxylic acid {1-[7-(2-methyl-1H-indol-5-ylamino)-thieno[3,2-b]pyridine-2-carbonyl]-pyrrolidin-3-yl}-amide

6-Amino-3-aza-bicyclo[3.1.0]hex-3-yl)-[7-(2-methyl-1H-indol-5-ylamino)-thieno[3,2-b]pyridin-2-yl]-methanone

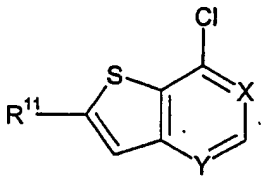
(3S)-(3-Methoxy-pyrrolidin-1-yl)-[7-(2-methyl-1H-indol-5-ylamino)-thieno[3,2-b]pyridin-2-yl]-methanone; pharmaceutically acceptable salts of said compounds; solvates of said compounds; and prodrugs of said compounds.

In one embodiment of the invention relates to a method of preparing a compound of the formula **1**



1

or a pharmaceutically acceptable salt, prodrug or hydrate thereof, which comprises treating a compound of formula 22



22

with HNR^1R^2 wherein X, Y, R^1, R^2, and R^{11} are as defined above.

In one preferred embodiment of the aforementioned method Y is N.

The invention also relates to a pharmaceutical composition for the treatment of pancreatitis or kidney disease (including proliferative glomerulonephritis and diabetes-induced renal disease) in a mammal which comprises a therapeutically effective amount of a compound of formula **1**, or a pharmaceutically acceptable salt, prodrug or hydrate thereof, and a pharmaceutically acceptable carrier.

The invention also relates to a pharmaceutical composition for the prevention of blastocyte implantation in a mammal which comprises a therapeutically effective amount of a compound of formula **1**, or a pharmaceutically acceptable salt, prodrug or hydrate thereof, and a pharmaceutically acceptable carrier.

The invention also relates to a pharmaceutical composition for treating a disease related to vasculogenesis or angiogenesis in a mammal which comprises a therapeutically effective amount of a compound of formula **1**, or a pharmaceutically acceptable salt, prodrug or hydrate thereof, and a pharmaceutically acceptable carrier. In ne embodiment, said pharmaceutical

composition is for treating a disease selected from the group consisting of tumor angiogenesis, chronic inflammatory disease such as rheumatoid arthritis, atherosclerosis, skin diseases such as psoriasis, excema, and scleroderma, diabetes, diabetic retinopathy, retinopathy of prematurity, age-related macular degeneration, hemangioma, glioma, melanoma, Kaposi's sarcoma and ovarian, breast, lung, pancreatic, prostate, colon and epidermoid cancer.

The invention also relates to a method of treating a hyperproliferative disorder in a mammal which comprises administering to said mammal a therapeutically effective amount of the compound of formula **1**, or a pharmaceutically acceptable salt, prodrug or hydrate thereof. In one embodiment, said method relates to the treatment of cancer such as brain, squamous cell, bladder, gastric, pancreatic, breast, head, neck, oesophageal, prostate, colorectal, lung, renal, kidney, ovarian, gynecological or thyroid cancer. In another embodiment, said method relates to the treatment of a non-cancerous hyperproliferative disorder such as benign hyperplasia of the skin (e.g., psoriasis) or prostate (e.g., benign prostatic hypertropy (BPH)).

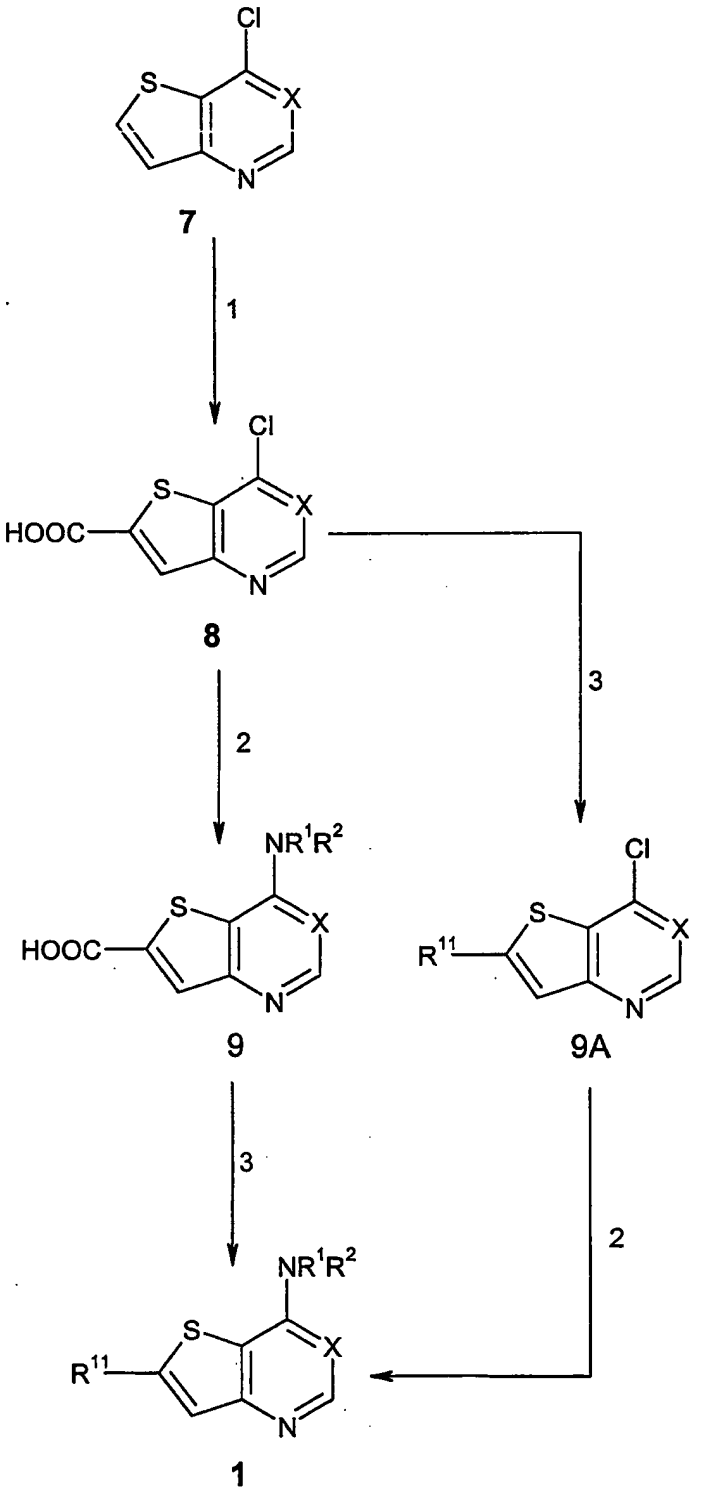
The invention also relates to a method for the treatment of a hyperproliferative disorder in a mammal which comprises administering to said mammal a therapeutically effective amount of a compound of formula **1**, or a pharmaceutically acceptable salt, prodrug or hydrate thereof, in combination with an anti-tumor agent selected from the group consisting of, but not limited to, mitotic inhibitors, alkylating agents, anti-metabolites, intercalating agents, growth factor inhibitors, cell cycle inhibitors, enzymes, topoisomerase inhibitors, biological response modifiers, anti-hormones, kinase inhibitors, matrix metalloprotease inhibitors, genetic therapeutics and anti-androgens.

The invention also relates to a method of treating pancreatitis or kidney disease in a mammal which comprises administering to said mammal a therapeutically effective amount of a compound of formula **1**, or a pharmaceutically acceptable salt, prodrug or hydrate thereof.

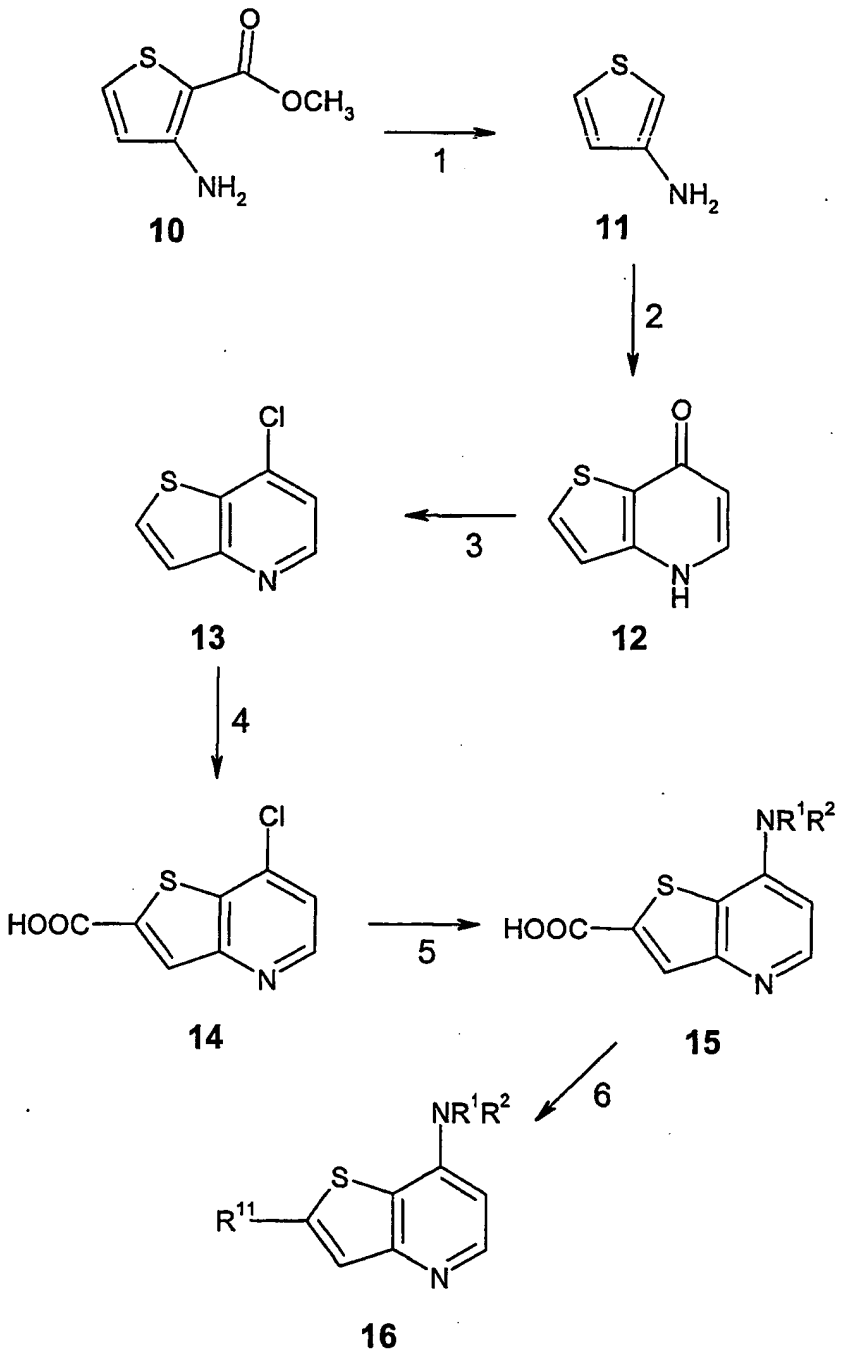
The invention also relates to a method of preventing blastocyte implantation in a mammal which comprises administering to said mammal a therapeutically effective amount of a compound of formula **1**, or a pharmaceutically acceptable salt, prodrug or hydrate thereof.

The invention also relates to a method of treating diseases related to vasculogenesis or angiogenesis in a mammal which comprises administering to said mammal an effective amount of a compound of formula **1**, or a pharmaceutically acceptable salt, prodrug or hydrate thereof. In one embodiment, said method is for treating a disease selected from the group consisting of tumor angiogenesis, chronic inflammatory disease such as rheumatoid arthritis, atherosclerosis, skin diseases such as psoriasis, excema, and scleroderma, diabetes, diabetic retinopathy, retinopathy of prematurity, age-related macular degeneration, hemangioma, glioma, melanoma, Kaposi's sarcoma and ovarian, breast, lung, pancreatic, prostate, colon and epidermoid cancer.

Scheme 1



Scheme 2


O
S
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NH2
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Cl
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HOOC
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NR1R2
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HOOC
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NR1R2
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R11
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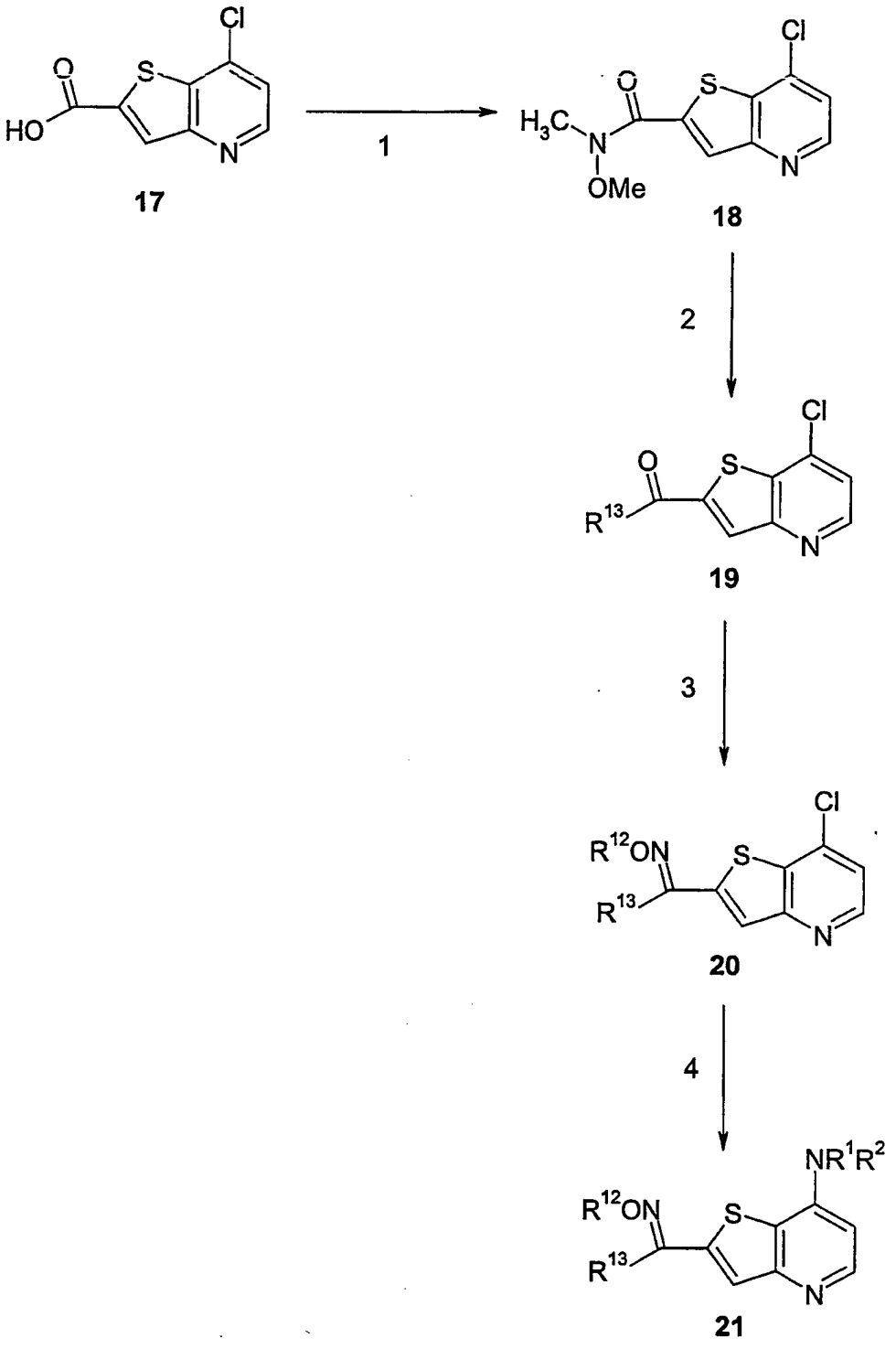
16

Scheme 3



coloring matters or dyes and, if desired, emulsifying agents or suspending agents, together with diluents such as water, ethanol, propylene glycol, glycerin, or combinations thereof.

Methods of preparing various pharmaceutical compositions with a specific amount of active compound are known, or will be apparent, to those skilled in this art. For examples, see Remington's Pharmaceutical Sciences, Mack Publishing Company, Easter, Pa., 15th Edition (1975).

The examples and preparations provided below further illustrate and exemplify the compounds of the present invention and methods of preparing such compounds. It is to be understood that the scope of the present invention is not limited in any way by the scope of the following examples and preparations.

The examples and preparations provided below further illustrate and exemplify the compounds of the present invention and methods of preparing such compounds. It is to be understood that the scope of the present invention is not limited in any way by the scope of the following examples and preparations.

Where HPLC chromatography is referred to in the preparations and examples below, the general conditions used, unless otherwise indicated, are as follows. The column used is a ODS Hypersil column (manufactured by Hewlett Packard) of 150 mm length and 4.0 mm interior diameter. The samples are run on a Hewlett Packard-1050 system. A gradient solvent method is used running 100 percent ammonium acetate / acetic acid buffer (0.2 M) to 100 percent acetonitrile over 10 minutes. The system then proceeds on a wash cycle with 100 percent acetonitrile for 1.5 minutes and then 100 percent buffer solution for 3 minutes. The flow rate over this period is a constant 3 ml / minute. Peak detection is carried out with a diode array detector at 254 and 300 nM wavelengths.

Example 1

A. Lithium 7-chloro-thieno[3,2-b]pyridine-2-carboxylate

n-Butyllithium (0.13 mol, 52 mL) was added dropwise to a solution of 7-chloro-thieno[3,2-b]pyridine (20 g, 0.12 mol) in THF (200 mL) at –78 °C, and the internal temperature was kept below -70 °C. After 1 h the yellow solution was quenched with $CO_{2(g)}$ until a white suspension resulted. The resulting mixture was allowed to warm to room temperature, then concentrated under reduced pressure to give a white solid. The resulting solid was triturated with ether then dried *in-vacuo* to afford the title compound as a white solid (23.5 g, 90%). MS: 213 (MH+); HPLC Rf: 2.50 min; HPLC purity: 94%.

B. (7-chloro-thieno[3,2-b]pyridin-2-yl)-pyrrolidin-1-yl-methanone

A solution of lithium 7-chloro-thieno[3,2-b]pyridine-2-carboxylate (0.50 g, 2.4 mmol), thionyl chloride (3.5 mmol, 1.8 ml), CH_2Cl_2 (20 ml), and DMF (0.2 ml) was heated to reflux. After 3 h the resulting yellow solution was concentrated under reduced pressure, and the residue was suspended in CH_2Cl_2 (20 mL). Pyrrolidine (2.35 mmol, 167 mg) was then added dropwise. After 12h the reaction mixture was concentrated onto silica gel (5 mL) and purified by flash chromatography on silica gel eluting with CH_2Cl_2/MeOH (97/3) to afford the title compound as a white solid (360 mg, 57%). MS: 266.9/268.9 (MH+); HPLC Rf: 4.51 min; HPLC purity: 98 %.

C. [7-(2-Methyl-1H-indol-5-ylamino)-thieno[3,2-b]pyridin-2-yl]-pyrrolidin-1-yl-methanone

A solution of (7-chloro-thieno[3,2-b]pyridin-2-yl)-pyrrolidin-1-yl-methanone (0.359 g, 1.34 mmol) and 2-methyl-1H-indol-5-ylamine (0.19 g, 1.3 mmol) in EtOH (10 mL) was heated to reflux for 48 h. The reaction mixture was cooled to room temperature and concentrated onto silica gel (5 mL). Purification by flash chromatography on silica gel eluting with CH_2Cl_2/NEt_3 (99.5/0.5) afforded the title compound as a yellow solid (550 mg) MS: 377.2 (MH+); HPLC Rf: 4.45 min; HPLC purity: 97 %.

Example 2

A. 7-Chloro-thieno[3,2-b]pyridine-2-carboxylic acid ethylamide

The title compound was prepared from ethylamine and lithium 7-chloro-thieno[3,2-b]pyridine-2-carboxylate by a procedure analogous to Example 1B. MS: n.d.; HPLC Rf: 4.18 min; HPLC purity: 98%.

B. 7-(2-Methyl-1H-indol-5-ylamino)-thieno[3,2-b]pyridine-2-carboxylic acid ethylamide

The title compound was prepared from 2-methyl-1H-indol-5-ylamine and 7-Chloro-thieno[3,2-b]pyridine-2-carboxylic acid ethylamide by a procedure analogous to Example 1C. MS: 351 (MH+); HPLC Rf: 4.33 min; HPLC purity: 98%.

Example 3

A. 7-Chloro-thieno[3,2-b]pyridine-2-carboxylic acid amide

A solution of lithium 7-chloro-thieno[3,2-b]pyridine-2-carboxylate (1.0 g, 4.7 mmol), thionyl chloride (7.0 mmol, 3.5 mL), CH_2Cl_2 (40 mL), and DMF (0.4 mL) was heated to reflux. After 3 h the resulting yellow solution was concentrated under reduced pressure, the resulting residue was suspended in CH_2Cl_2 (60 mL), and NH_3 gas was bubbled through the mixture for 10 min. The reaction mixture was filt red to give the title compound as a white solid (1.17 g, 100%). MS: 213.0/215.1 (MH+); HPLC Rf: 3.44 min; HPLC purity: 98%.

B. 7-(2-Methyl-1H-indol-5-ylamino)-thieno[3,2-b]pyridine-2-carboxylic acid amide

The title compound was prepared from 2-methyl-1H-indol-5-ylamine and 7-chloro-thieno[3,2-b]pyridine-2-carboxylic acid amide by a procedure analogous to Example 1C. MS: 323 (MH+); HPLC Rf: 3.65 min; HPLC purity: 98%.

Example 4

A. 7-Chloro-thieno[3,2-b]pyridine-2-carboxylic acid dimethylamide

The title compound was prepared from dimethyl amine and lithium 7-chloro-thieno[3,2-b]pyridine-2-carboxylate by a procedure analogous to Example 1B. MS: 239/241 (MH+); HPLC Rf: n.d.; HPLC purity: n.d.

B. 7-(2-Methyl-1H-indol-5-ylamino)-thieno[3,2-b]pyridine-2-carboxylic acid dimethylamide

The title compound was prepared from 2-methyl-1H-indol-5-ylamine and 7-chloro-thieno[3,2-b]pyridine-2-carboxylic acid dimethylamide by a procedure analogous to Example 1C. MS: 351 (MH+); HPLC Rf: 3.87 min.; HPLC purity: 94%.

Example 5

A. 7-Chloro-thieno[3,2-b]pyridine-2-carboxylic acid (pyridin-3-ylmethyl)-amide

The title compound was prepared from 3-aminomethylpyridine and lithium 7-chloro-thieno[3,2-b]pyridine-2-carboxylate by a procedure analogous to Example 1B. MS: n.d.; HPLC Rf: n.d.; HPLC purity: n.d.

B. 7-(2-Methyl-1H-indol-5-ylamino)-thieno[3,2-b]pyridine-2-carboxylic acid (pyridin-3-ylmethyl)-amide

The title compound was prepared from 2-methyl-1H-indol-5-ylamine and 7-chloro-thieno[3,2-b]pyridine-2-carboxylic acid (pyridin-3-ylmethyl)-amide by a procedure analogous to Example 1C. MS: 414 (MH+), HPLC Rf: 4.12 min.; HPLC purity: 97%.

Example 6

A. 7-Chloro-thieno[3,2-b]pyridine-2-carboxylic acid methylamide

The title compound was prepared from methylamine and lithium 7-chloro-thieno[3,2-b]pyridine-2-carboxylate by a procedure analogous to Example 1B. MS: n.d.; HPLC Rf: 3.70 min.; HPLC purity: 89%.

B. 7-(2-Methyl-1H-indol-5-ylamino)-thieno[3,2-b]pyridine-2-carboxylic acid methylamide

The title compound was prepared from 2-methyl-1H-indol-5-ylamine and 7-Chloro-thieno[3,2-b]pyridine-2-carboxylic acid methylamide by a procedure analogous to Example 1C. MS: 337 (MH+); HPLC Rf: 3.86 min.; HPLC purity: 98%.

Example 7

A. 7-Chloro-thieno[3,2-b]pyridine-2-carboxylic acid (pyridin-2-ylmethyl)-amide

The title compound was prepared from 2-aminomethylpyridine and lithium 7-chloro-thieno[3,2-b]pyridine-2-carboxylate by a procedure analogous to Example 1B. MS: 304/306 (MH+); HPLC Rf: 4.36 min.; HPLC purity: 97%.

B. 7-(2-Methyl-1H-indol-5-ylamino)-thieno[3,2-b]pyridine-2-carboxylic acid (pyridin-2-ylmethyl)-amide

The title compound was prepared from 2-methyl-1H-indol-5-ylamine and 7-chloro-thieno[3,2-b]pyridine-2-carboxylic acid (pyridin-2-ylmethyl)-amide by a procedure analogous to Example 1C. MS: 414 (MH+); HPLC Rf: 4.34 min.; HPLC purity: 97%.

Example 8

A. 7-Chloro-thieno[3,2-b]pyridine-2-carboxylic acid (2-dimethylamino-ethyl)-amide

The title compound was prepared from 2-dimethylaminoethyl amine and lithium 7-chloro-thieno[3,2-b]pyridine-2-carboxylate by a procedure analogous to Example 1B. MS: 284/286 (MH+); HPLC Rf: 3.47 min.; HPLC purity: 95%.

B. 7-(2-Methyl-1H-indol-5-ylamino)-thieno[3,2-b]pyridine-2-carboxylic acid (2-dimethylamino-ethyl)-amide

The title compound was prepared from 2-methyl-1H-indol-5-ylamine and 7-chloro-thieno[3,2-b]pyridine-2-carboxylic acid (2-dimethylamino-ethyl)-amide by a procedure analogous to Example 1C. MS: 394 (MH+), HPLC Rf: 3.43; HPLC purity: 98%.

Example 9

A. 7-Chloro-thieno[3,2-b]pyridine-2-carboxylic acid [3-(4-methyl-piperazin-1-yl)-propyl]-amide

The title compound was prepared from 3-(4-methylpiperazin-1-yl)-propylamine and lithium 7-chloro-thieno[3,2-b]pyridine-2-carboxylate by a procedure analogous to Example 1B. MS: 353/355 (MH+); HPLC Rf: n.d.; HPLC purity: n.d.

B. 7-(2-Methyl-1H-indol-5-ylamino)-thieno[3,2-b]pyridine-2-carboxylic acid [3-(4-methyl-piperazin-1-yl)-propyl]-amide

The title compound was prepared from 2-methyl-1H-indol-5-ylamine and 7-chloro-thieno[3,2-b]pyridine-2-carboxylic acid [3-(4-methyl-piperazin-1-yl)-propyl]-amide by a procedure analogous to Example 1C. MS: 463 (MH+), HPLC Rf: 3.41 min.; HPLC purity: 99%.

Example 10

A. 7-Chloro-thieno[3,2-b]pyridine-2-carboxylic acid (3-morpholin-4-yl-propyl)-amide

The title compound was prepared from 3-morpholin-4-ylpropylamine and lithium 7-chloro-thieno[3,2-b]pyridine-2-carboxylate by a procedure analogous to Example 1B. MS: 340/342 (MH+); HPLC Rf: 3.45 min.; HPLC purity: 89%.

B. 7-(2-Methyl-1H-indol-5-ylamino)-thieno[3,2-b]pyridine-2-carboxylic acid (3-morpholin-4-yl-propyl)-amide

The title compound was prepared from 2-methyl-1H-indol-5-ylamine and 7-chloro-thieno[3,2-b]pyridine-2-carboxylic acid (3-morpholin-4-yl-propyl)-amide by a procedure analogous to Example 1C. MS: 450 (MH+); HPLC Rf: 3.48 min.; HPLC purity 96%.

Example 11

A. 7-Chloro-thieno[3,2-b]pyridine-2-carboxylic acid (pyridin-4-ylmethyl)-amide

The title compound was prepared from 4-aminomethyl pyridine and lithium 7-chloro-thieno[3,2-b]pyridine-2-carboxylate by a procedure analogous to Example 1B. MS: 304/306 (MH+); HPLC Rf: 4.08 min.; HPLC purity: 78%.

B. 7-(2-Methyl-1H-indol-5-ylamino)-thieno[3,2-b]pyridine-2-carboxylic acid (pyridin-4-ylmethyl)-amide

The title compound was prepared from 2-methyl-1H-indol-5-ylamine and 7-chloro-thieno[3,2-b]pyridine-2-carboxylic acid (pyridin-4-ylmethyl)-amide by a procedure analogous to Example 1C. MS: 414 (MH+), HPLC Rf: 3.97 min.; HPLC purity 94%.

Example 12

A. 7-Chloro-thieno[3,2-b]pyridine-2-carboxylic acid (2-pyridin-2-yl-ethyl)-amide

The title compound was prepared from 2-pyridine-2-yl-ethylamine pyridine and lithium 7-chloro-thieno[3,2-b]pyridine-2-carboxylate by a procedure analogous to Example 1B. MS: 318/320 (MH+); HPLC Rf: 4.33 min.; HPLC purity: 97%.

B. . 7-(2-Methyl-1H-indol-5-ylamino)-thieno[3,2-b]pyridine-2-carboxylic acid (2-pyridin-2-yl-ethyl)-amide

The title compound was prepared from 2-methyl-1H-indol-5-ylamine and 7-chloro-thieno[3,2-b]pyridine-2-carboxylic acid (2-pyridin-2-yl-ethyl)-amide by a procedure analogous to Example 1C. MS: 428 (MH+), HPLC Rf: 4.33 min; HPLC purity 99%.

Example 13

A. 7-Chloro-thieno[3,2-b]pyridine-2-carboxylic acid pyridin-4-ylamide

The title compound was prepared from 4-aminopyridine and lithium 7-chloro-thieno[3,2-b]pyridine-2-carboxylate by a procedure analogous to Example 1B. MS: 290/292 (MH+); HPLC Rf: 4.63 min.; HPLC purity: 99%.

B. 7-(2-Methyl-1H-indol-5-ylamino)-thieno[3,2-b]pyridine-2-carboxylic acid pyridin-4-ylamide

The title compound was prepared from 2-methyl-1H-indol-5-ylamine and 7-chloro-thieno[3,2-b]pyridine-2-carboxylic acid pyridin-4-ylamide by a procedure analogous to Example 1C. MS: 400 (MH+); HPLC Rf: 4.24 min.; HPLC purity: 99%.

Example 14

A. 7-Chloro-thieno[3,2-b]pyridine-2-carboxylic acid (2-morpholin-4-yl-ethyl)-amide

The title compound was prepared from 2-morpholine-4-yl-ethylamine and lithium 7-chloro-thieno[3,2-b]pyridine-2-carboxylate by a procedure analogous to Example 1B. MS: 326/328 (MH+); HPLC Rf: 3.45 min.; HPLC purity 94%.

B. 7-(2-Methyl-1H-indol-5-ylamino)-thieno[3,2-b]pyridine-2-carboxylic acid (2-morpholin-4-yl-ethyl)-amide

The title compound was prepared from 2-methyl-1H-indol-5-ylamine and 7-chloro-thieno[3,2-b]pyridine-2-carboxylic acid (2-morpholin-4-yl-ethyl)-amide by a procedure analogous to Example 1C. MS: 436 (MH+); HPLC Rf: 3.45 min.; HPLC purity 94%.

Example 15

A. 7-Chloro-thieno[3,2-b]pyridine-2-carboxylic acid (2-pyridin-4-yl-ethyl)-amide

The title compound was prepared from 2-pyridin-4-yl-ethyl amine and lithium 7-chloro-thieno[3,2-b]pyridine-2-carboxylate by a procedure analogous to Example 1B. MS: 318/320 (MH+); HPLC Rf: 4.08 min.; HPLC purity 99%.

B. 7-(2-Methyl-1H-indol-5-ylamino)-thieno[3,2-b]pyridine-2-carboxylic acid (2-pyridin-4-yl-ethyl)-amide

The title compound was prepared from 2-methyl-1H-indol-5-ylamine and 7-chloro-thieno[3,2-b]pyridine-2-carboxylic acid (2-pyridin-4-yl-ethyl)-amide by a procedure analogous to Example 1C. MS: 428 (MH+); HPLC Rf: 4.09 min.; HPLC purity 99%.

Example 16

A. 7-Chloro-thieno[3,2-b]pyridine-2-carboxylic acid (2-piperidin-1-yl-ethyl)-amide

The title compound was prepared from 2-piperidin-1-yl-ethyl amine and lithium 7-chloro-thieno[3,2-b]pyridine-2-carboxylate by a procedure analogous to Example 1B. MS: 324/326 (MH+); HPLC Rf: 3.64 min.; HPLC purity 93%.

B. 7-(2-Methyl-1H-indol-5-ylamino)-thieno[3,2-b]pyridine-2-carboxylic acid (2-piperidin-1-yl-ethyl)-amide

The title compound was prepared from 2-methyl-1H-indol-5-ylamine and 7-chloro-thieno[3,2-b]pyridine-2-carboxylic acid (2-piperidin-1-yl-ethyl)-amide by a procedure analogous to Example 1C. MS: 434 (MH+); HPLC Rf: 3.82 min.; HPLC purity 99%.

Example 17

A. 7-Chloro-thieno[3,2-b]pyridine-2-carboxylic acid pyridin-3-ylamide

The title compound was prepared from 3-aminopyridine and lithium 7-chloro-thieno[3,2-b]pyridine-2-carboxylate by a procedure analogous to Example 1B. MS: 290/292 (MH+), HPLC Rf: 4.72 min.; HPLC purity 95%.

B. 7-(2-Methyl-1H-indol-5-ylamino)-thieno[3,2-b]pyridine-2-carboxylic acid pyridin-3-ylamide

The title compound was prepared from 2-methyl-1H-indol-5-ylamine and 7-chloro-thieno[3,2-b]pyridine-2-carboxylic acid pyridin-3-ylamide by a procedure analogous to Example 1C. MS: 400 (MH+), HPLC Rf: 4.58 min.; HPLC purity 99%.

Example 18

A. 7-Chloro-thieno[3,2-b]pyridine-2-carboxylic acid (2-pyridin-3-yl-ethyl)-amide

The title compound was prepared from 2-pyridine-3-yl-ethyl amine and lithium 7-chloro-thieno[3,2-b]pyridine-2-carboxylate by a procedure analogous to Example 1B. MS: 318/320 (MH+); HPLC Rf: 4.27 min.; HPLC purity 76%.

B. 7-(2-Methyl-1H-indol-5-ylamino)-thieno[3,2-b]pyridine-2-carboxylic acid (2-pyridin-3-yl-ethyl)-amide

The title compound was prepared from 2-methyl-1H-indol-5-ylamine and 7-chloro-thieno[3,2-b]pyridine-2-carboxylic acid (2-pyridin-3-yl-ethyl)-amide by a procedure analogous to Example 1C. MS: 428 (MH+); HPLC Rf: 4.34 min.; HPLC purity 99%.

Example 19

A. 7-Chloro-thieno[3,2-b]pyridin-2-yl-morpholin-4-yl-methanone

The title compound was prepared from morpholine and lithium 7-chloro-thieno[3,2-b]pyridine-2-carboxylate by a procedure analogous to Example 1B. MS: 282/284 (MH+), HPLC Rf: 3.96 min.; HPLC purity 98%.

B. [7-(2-Methyl-1H-indol-5-ylamino)-thieno[3,2-b]pyridin-2-yl]-morpholin-4-yl-methanone

The title compound was prepared from 2-methyl-1H-indol-5-ylamine and 7-chloro-thieno[3,2-b]pyridin-2-yl-morpholin-4-yl-methanone by a procedure analogous to Example 1C. MS: 393 (MH+), HPLC Rf: 3.90 min.; HPLC purity 96%.

Example 20

A. 7-Chloro-thieno[3,2-b]pyridine-2-carbonitrile

n-Butyllithium (2.2 mmol, 0.88 mL) was added dropwise to a solution of 7-chloro-thieno[3,2-b]pyridine (0.250 g, 1.48 mmol) in THF (10 mL) at –78 °C while the internal temperature was kept below –70 °C. After 1 h TsCN (0.804 mg, 4.44 mmol) was added. After 3 h the reaction was quenched with distilled water (10 mL), warmed to rt, and the layers were separated. The aqueous layer was further extracted with ethyl acetate (3 X 10 mL). The combined organic extracts were dried (Na_2SO_4), then concentrated under reduced pressure. Purification by flash chromatography using a Biotage 40 S column eluting with hexane/ethyl acetate (7/3) afforded the title compound as a white solid (92 mg, 32%). MS: 195/197 (MH+); HPLC Rf: 4.89 min; HPLC purity: 85%.

B. 7-(2-Methyl-1H-indol-5-ylamino)-thieno[3,2-b]pyridine-2-carbonitrile

The title compound was prepared from 2-methyl-1H-indol-5-ylamine and 7-chloro-thieno[3,2-b]pyridine-2-carbonitrile by a procedure analogous to Example 1C. MS: 305 (MH+), HPLC Rf: 4.86 min.; HPLC purity: 85%.

Example 21

A. 7-(2-Methyl-1H-indol-5-ylamino)-thieno[3,2-b]pyridine-2-carboxylic acid

Lithium 7-chloro-thieno[3,2-b]pyridine-2-carboxylate carboxylate (1.00 g, 4.68 mmole) and 2-methyl-1H-indol-5-ylamine (822 mg, 5.62 mmole) were dissolved in a mixture of ethanol (90 mL) and dichloroethane (10 mL). The reaction mixture was heated at reflux for 40 hours. Upon cooling, a yellow precipitate formed, which was collected by filtration and washed with ether. After drying under vacuum, the title compound was obtained as yellow powder (1.13 g, 75%). MS: 324 (MH+); HPLC Rf: 3.10min; HPLC purity: 97%.

B. (+/-)-(3-Hydroxy-pyrrolidin-1-yl)[7-(2-methyl-1H-indol-5-ylamino)-thieno[3,2-b]pyridin-2-yl]-methanone

To a solution of 7-(2-methyl-1H-indol-5-ylamino)-thieno[3,2-b]pyridine-2-carboxylic acid (0.10 g, 0.31 mmol), HATU (0.17 g, 0.46 mmol) and DMAP (0.040 g, 0.31 mmol) in DMF (3 mL) was added racemic 3-hydroxy-pyrrolidine (0.040 g, 0.46 mmol). After 3 h the reaction was quenched with a saturated aqueous solution of $NaHCO_3$ (10 mL) and EtOAC (10 mL). The aqueous layer was further extracted with EtOAC (2 x 10 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated under reduced pressure. Purification by flash chromatography on silica gel (CH_2Cl_2/MeOH 85:15) afforded the title compound as a yellow solid (0.093 g, 76%). MS: 393 (MH+); HPLC Rf: 3.41; HPLC purity: 87%.

Examples 22-60

Compounds from examples 22-60 were synthesized by one of two methods. Method A is a two-step method analogous to that described in Example 1B/C. In each case, a commercially available amine was coupled to lithium 7-chloro-thieno[3,2-b]pyridine-2-carboxylate by a procedure analogous to Example 1B, and the resulting amides were treated with 2-methyl-1H-indole-5-ylamine according to Example 1C to give the title compounds. Method B involves the coupling of an amine to 7-(2-methyl-1H-indol-5-ylamino)-thieno[3,2-b]pyridine-2-carboxylic acid by a method analogous to Example 21B.

Example Number	Compound Name	Method	MS (MH+)	HPLC purity	HPLC Rf (min)
22	7-(2-Methyl-1H-indol-5-ylamino)-thieno[3,2-b]pyridine-2-carboxylic acid methyl-pyridin-3-ylmethyl-amide	A	428	93	4.08
23	[7-(2-Methyl-1H-indol-5-ylamino)-thieno[3,2-b]pyridin-2-yl]-(4-methyl-piperazin-1-yl)-methanone	A	406	99	3.13
24	7-(2-Methyl-1H-indol-5-ylamino)-thieno[3,2-b]pyridine-2-carboxylic acid thiazol-2-ylamide	A	406	98	4.79
25	7-(2-Methyl-1H-indol-5-ylamino)-thieno[3,2-b]pyridine-2-carboxylic acid diethylamide	A	379	95	4.54
26	7-(2-Methyl-1H-indol-5-ylamino)-thieno[3,2-b]pyridine-2-carboxylic acid ethyl-methyl-amide	A	365	97	4.15

27	Azetidin-1-yl-[7-(2-methyl-1H-indol-5-ylamino)-thieno[3,2-b]pyridin-2-yl]-methanone	A	363	99	4.07
28	(3,4-Dihydro-1H-isoquinolin-2-yl)-[7-(2-methyl-1H-indol-5-ylamino)-thieno[3,2-b]pyridin-2-yl]-methanone	AA	439	98	5.47
29	CP-702055-01: 7-(2-Methyl-1H-indol-5-ylamino)-thieno[3,2-b]pyridine-2-carboxylic acid (2-dimethylamino-ethyl)-methyl-amide	A	408	99	3.37
30	7-(2-Methyl-1H-indol-5-ylamino)-thieno[3,2-b]pyridine-2-carboxylic acid cyclohexyl-methyl-amide	A	419	98	5.47
31	7-(2-Methyl-1H-indol-5-ylamino)-thieno[3,2-b]pyridine-2-carboxylic acid cyclohexylamide	A	405	98	5.74
32	Aziridin-1-yl-[7-(2-methyl-1H-indol-5-ylamino)-thieno[3,2-b]pyridin-2-yl]-methanone	A	349	99	4.60
33	(2S)-(2-Methoxymethyl-pyrrolidin-1-yl)-[7-(2-methyl-1H-indol-5-ylamino)-thieno[3,2-b]pyridin-2-yl]-methanone	A	421	99	4.55
34	(2,5-Dimethyl-pyrrolidin-1-yl)-[7-(2-methyl-1H-indol-5-ylamino)-thieno[3,2-b]pyridin-2-yl]-methanone	A	405	95	5.28
35	(2,6-Dimethyl-piperidin-1-yl)-[7-(2-methyl-1H-indol-5-ylamino)-thieno[3,2-b]pyridin-2-yl]-methanone	A	419	95	5.43
36	(+/-)-N-{1-[7-(2-Methyl-1H-indol-5-ylamino)-thieno[3,2-b]pyridine-2-carbonyl]-pyrrolidin-3-yl}-acetamide	A	434	93	3.72
37	(+/-)-N-Ethyl-N-{1-[7-(2-methyl-1H-indol-5-ylamino)-thieno[3,2-b]pyridine-2-carbonyl]-pyrrolidin-3-yl}-acetamide	A	462	92	4.14
38	CP-708103-01: 7-(2-Methyl-1H-indol-5-ylamino)-thieno[3,2-b]pyridine-2-carboxylic acid diisopropylamide	A	407	98	5.66
39	1-[7-(2-Methyl-1H-indol-5-ylamino)-thieno[3,2-b]pyridine-2-carbonyl]—(2S)-pyrrolidine-2-	A	420	95	3.47

	carboxylic acid amide				
40	[7-(2-Methyl-1H-indol-5-ylamino)-thieno[3,2-b]pyridin-2-yl]-thiomorpholin-4-yl-methanone	A	409	95	4.72
41	(+/-)-1-[7-(2-Methyl-1H-indol-5-ylamino)-thieno[3,2-b]pyridine-2-carbonyl]-piperidine-3-carboxylic acid ethyl ester	A	463	97	5.17
42	(+/-)-(3-Methylamino-pyrrolidin-1-yl)-[7-(2-methyl-1H-indol-5-ylamino)-thieno[3,2-b]pyridin-2-yl]-methanone	A	406	90	3.56
43	1-[7-(2-Methyl-1H-indol-5-ylamino)-thieno[3,2-b]pyridine-2-carbonyl]-pyrrolidine-(2S)-2-carboxylic acid dimethylamide	A	448	96	4.06
44	7-(2-Methyl-1H-indol-5-ylamino)-thieno[3,2-b]pyridine-2-carboxylic acid (2-methoxy-ethyl)-methyl-amide	A	395	92	4.26
45	7-(2-Methyl-1H-indol-5-ylamino)-thieno[3,2-b]pyridine-2-carboxylic acid (2,2,2-trifluoro-ethyl)-amide	A	405	98	5.13
46	(3S)-(3-Dimethylamino-pyrrolidin-1-yl)-[7-(2-methyl-1H-indol-5-ylamino)-thieno[3,2-b]pyridin-2-yl]-methanone	A	420	99	3.67
47	(3S)-(3-Amino-pyrrolidin-1-yl)-[7-(2-methyl-1H-indol-5-ylamino)-thieno[3,2-b]pyridin-2-yl]-methanone	A	392	99	3.30
48	1-[7-(2-Methyl-1H-indol-5-ylamino)-thieno[3,2-b]pyridine-2-carbonyl]-pyrrolidine-(2S)-2-carboxylic acid	A	421	84	3.32
49	7-(2-Methyl-1H-indol-5-ylamino)-thieno[3,2-b]pyridine-2-carboxylic acid bis-(2,2,2-trifluoro-ethyl)-amide	A	487	90	5.74
50	(+/-)-N-Methyl-N-{1-[7-(2-methyl-1H-indol-5-ylamino)-thieno[3,2-b]pyridine-2-carbonyl]-pyrrolidin-3-yl}-acetamide	A	448	97	3.88
51	(3R)-(3-Dimethylamino-pyrrolidin-1-yl)-[7-(2-methyl-1H-indol-5-ylamino)-thieno[3,2-	A	420	99	3.82

	b]pyridin-2-yl]-methanone				
52	(2R)-(2-Methoxymethyl-pyrrolidin-1-yl)-[7-(2-methyl-1H-indol-5-ylamino)-thieno[3,2-b]pyridin-2-yl]-methanone	B	421	96	4.61
53	(+/-)-(3-Hydroxy-pyrrolidin-1-yl)-[7-(2-methyl-1H-indol-5-ylamino)-thieno[3,2-b]pyridin-2-yl]-methanone	B	393	91	3.57
54	(2R)-(2-Hydroxymethylpyrrolidin-1-yl)-[7-(2-methyl-1H-indol-5-ylamino)-thieno[3,2-b]pyridin-2-yl]-methanone	B	407	88	3.20
55	(2S)-(2-Hydroxymethyl-pyrrolidin-1-yl)-[7-(2-methyl-1H-indol-5-ylamino)-thieno[3,2-b]pyridin-2-yl]-methanone	B	407	95	3.47
56	(3S)-(3-Hydroxy-pyrrolidin-1-yl)-[7-(2-methyl-1H-indol-5-ylamino)-thieno[3,2-b]pyridin-2-yl]-methanone	B	393	92	2.97
57	(3R)-(3-Hydroxy-pyrrolidin-1-yl)-[7-(2-methyl-1H-indol-5-ylamino)-thieno[3,2-b]pyridin-2-yl]-methanone	B	393	94	3.68
58	(6-Hydroxymethyl-3-aza-bicyclo[3.1.0]hex-3-yl)-[7-(2-methyl-1H-indol-5-ylamino)-thieno[3,2-b]pyridin-2-yl]-methanone	B	419	95	3.74
59	[7-(2-Methyl-1H-indol-5-ylamino)-thieno[3,2-b]pyridin-2-yl]-piperidin-1-yl-methanone	B	391	98%	4.72
60	(3,4-Dihydroxy-pyrrolidin-1-yl)-[7-(2-methyl-1H-indol-5-ylamino)-thieno[3,2-b]pyridin-2-yl]-methanone	B	409	92	3.31

Example 61

A. 7-Chloro-thieno[3,2-b]pyridine-2-carboxylic acid methyl-pyridin-4-ylmethyl-amide

NaH (0.244 g, 6.09 mmol) was added to a solution of 7-chloro-thieno[3,2-b]pyridin-2-carboxylic acid (pyridin-4-ylmethyl)-amide (0.616 g, 2.03 mmol, prepared as described in Example 11) in DMF (10 mL). When the effervescence ceased, MeI (0.576 g, 4.06 mmol) was added dropwise. After 3 h the reaction mixture was quenched with saturated aqueous KCN (10 mL). The aqueous layer was xtracted with CH_2Cl_2 (3 x 10 mL). The combined organic extracts

were dried (Na_2SO_4), and the solvent was removed und r reduced pressure. Purification by flash chromatography on silica gel (CH_2Cl_2/MeOH 94:6) afforded the title compound as a yellow oil (0.15 g, 23%). MS: 318.0/320.0 (MH+); HPLC Rf: 4.24 min; HPLC purity: 93%.

B. 7-(2-Methyl-1H-indol-5-ylamino)-thieno[3,2-b]pyridine-2-carboxylic acid methyl-pyridin-4-ylmethyl-amide

The title compound was prepared from 7-chloro-thieno[3,2-b]pyridine-2-carboxylic acid methyl-pyridin-4-ylmethyl-amide and 2-methyl-1H-indol-5-ylamine by a method analogous to Example 1C. MS: 428 (MH+); HPLC Rf: 4.26 min; HPLC purity: 93%.

Example 62

A. 7-Chloro-thieno[3,2-b]pyridine-2-carboxylic acid methyl-pyridin-2-ylmethyl-amide

The title compound was prepared from MeI and 7-chloro-thieno[3,2-b]pyridine-2-carboxylic acid (pyridin-2-ylmethyl)-amide (Example 7A) as described in Example 61A. MS: 318/320 (MH+); HPLC Rf: 4.40 min.; HPLC purity: 90%.

B. 7-(2-Methyl-1H-indol-5-ylamino)-thieno[3,2-b]pyridine-2-carboxylic acid methyl-pyridin-2-ylmethyl-amide

The title compound was prepared from 7-chloro-thieno[3,2-b]pyridine-2-carboxylic acid methyl-pyridin-2-ylmethyl-amide and 2-methyl-1H-indol-5-ylamine by a procedure analogous to Example 1C. MS: 428 (MH+); HPLC Rf: 4.30 min.; HPLC purity: 97%.

Example 63

A. 7-Chloro-thieno[3,2-b]pyridine-2-carboxylic acid methyl-(2-morpholin-4-yl-ethyl)-amide

The title compound was prepared from MeI and 7-chloro-thieno[3,2-b]pyridine-2-carboxylic acid (2-morpholin-4-yl-ethyl)-amide (Example 14A) by a procedure analogous to Example 61A. MS: 340/342 (MH+); HPLC Rf: 3.29 min.; HPLC purity 99%.

B. 7-(2-Methyl-1H-indol-5-ylamino)-thieno[3,2-b]pyridine-2-carboxylic acid methyl-(2-morpholin-4-yl-ethyl)-amide

The title compound was prepared from 7-chloro-thieno[3,2-b]pyridine-2-carboxylic acid methyl-(2-morpholin-4-yl-ethyl)-amide and 2-methyl-1H-indol-5-ylamine by a procedure analogous to Example 1C. MS: 450 (MH+), HPLC Rf: 3.58 min.; HPLC purity: 99%.

Example 64

A. (+/-)-[1-(7-Chloro-thieno[3,2-b]pyridine-2-carbonyl)-pyrrolidin-3-yl]-carbamic acid tert-butyl ester

The title compound was prepared from lithium 7-chloro-thieno[3,2-b]pyridine-2-carboxylate and racemic pyrrolidin-3-yl-carbamic acid tert butyl ester by a method analogous to Example 1B. MS: 382/384 (MH+); HPLC Rf: 5.21 min.; HPLC purity 99%.

B. (+/-)-(3-Amino-pyrrolidin-1-yl)-(7-chloro-thieno[3,2-b]pyridin-2yl)-methanone

HCl(g) was bubbled through a solution of [1-(7-chloro-thieno[3,2-b]pyridine-2-carbonyl)-pyrrolidin-3-yl]-carbamic acid tert-butyl ester (0.472 g, 1.23 mmol) in MeOH (10 mL). After 10 min, TLC (CH_2Cl_2/MeOH 9:1) showed the reaction to be complete. The reaction mixture was poured into Et_2O (50 mL), and a white precipitate formed. The white solid was collected by filtration and washed with Et_2O to afford the title compound. MS: 281.0/283.0 (MH+); HPLC Rf; 3.02 min; HPLC purity: 99 %.

C. (+/-)-Cyclobutanecarboxylic acid {1-[7-chloro-thieno[3,2-b]pyridine-2-carbonyl]-pyrrolidin-3-yl}-amide

To a solution of (3-amino-pyrrolidin-1-yl)-(7-chloro-thieno[3,2-b]pyridin-2yl)-methanone (0.40 g, 1.4 mmol) and DMAP (0.693 g, 5.68 mmol) in CH_2Cl_2 (20 mL) was added cyclobutane carboxylic acid chloride (0.20 g, 1.7 mmol). After 3 h the reaction was quenched with distilled water (10 mL). The aqueous layer was extracted with CH_2Cl_2 (2 x 10 mL). The combined organic extracts were dried (Na_2SO_4), and concentrated onto silica gel (5 mL). Purification by flash chromatography on silica gel (CH_2Cl_2/MeOH 97:3) afforded the title compound as a white solid (0.36 g, 69%). MS: 364/366 (MH+); HPLC Rf: 4.24 min; HPLC purity: 94%.

D. (+/-)-Cyclobutanecarboxylic acid {1-[7-(2-methyl-1H-indol-5-ylamino)-thieno[3,2-b]pyridine-2-carbonyl]-pyrrolidin-3-yl}-amide

The title compound was prepared from (+/-)-cyclobutanecarboxylic acid {1-[7-chloro-thieno[3,2-b]pyridine-2-carbonyl]-pyrrolidin-3-yl}-amide and 2-methyl-1H-indol-5-ylamine by a procedure analogous to Example 1C. MS: 474 (MH+); HPLC Rf: 4.37 min.; HPLC purity 97%.

Example 65

A. {3-[7-Chloro-thieno[3,2-b]pyridine-2-carbonyl]-3-aza-bicyclo[3.1.0]hex-6-yl}-carbamic acid tert-butyl ester

The title compound was prepared from (3-aza-bicyclo[3.1.0]hex-6-yl)-carbamic acid tert-butyl ester and lithium 7-chloro-thieno[3,2-b]pyridine-2-carboxylate by a procedure analogous to Example 1B. MS: 394/396 (MH+); HPLC Rf: 5.30 min.; HPLC purity: 72%.

B. {3-[7-(2-Methyl-1H-indol-5-ylamino)-thieno[3,2-b]pyridine-2-carbonyl]-3-aza-bicyclo[3.1.0]hex-6-yl}-carbamic acid tert-butyl ester

The title compound was prepared from {3-[7-chloro-thieno[3,2-b]pyridine-2-carbonyl]-3-aza-bicyclo[3.1.0]hex-6-yl}-carbamic acid tert-butyl ester and 2-methyl-1H-indol-5-ylamine by a procedure analogous to Example 1C. MS: 504 (MH+); HPLC Rf: 5.31 min.; HPLC purity 95%.

C. 6-Amino-3-aza-bicyclo[3.1.0]hex-3-yl)-[7-(2-methyl-1H-indol-5-ylamino)-thieno[3,2-b]pyridin-2-yl]-methanone

The title compound was prepared by treating {3-[7-(2-methyl-1H-indol-5-ylamino)-thieno[3,2-b]pyridine-2-carbonyl]-3-aza-bicyclo[3.1.0]hex-6-yl}-carbamic acid tert-butyl ester with HCl gas as described in Example 64B. MS: 404 (MH+); HPLC Rf: 3.42 min.; HPLC purity: 97%.

Example 66

A. 4-[7-Chloro-thieno[3,2-b]pyridine-2-carbonyl]-piperazine-1-carboxylic acid tert-butyl ester

The title compound was prepared from piperazine-1-carboxylic acid tert-butyl ester and lithium 7-chloro-thieno[3,2-b]pyridine-2-carboxylate by a procedure analogous to Example 1B. MS: 382/384 (MH+); HPLC Rf: 5.72 min.; HPLC purity 94%.

B. 4-[7-(2-Methyl-1H-indol-5-ylamino)-thieno[3,2-b]pyridine-2-carbonyl]-piperazine-1-carboxylic acid tert-butyl ester

The title compound was prepared from 4-[7-chloro-thieno[3,2-b]pyridine-2-carbonyl]-piperazine-1-carboxylic acid tert-butyl ester and 2-methyl-1H-indol-5-ylamine by a method analogous to Example 1C. MS: 492 (MH+); HPLC Rf: 5.42 min.; HPLC purity 95%.

C. [7-(2-Methyl-1H-indol-5-ylamino)-thieno[3,2-b]pyridin-2-yl]-piperazin-1-yl-methanone

The title compound was prepared by treating 4-[7-(2-methyl-1H-indol-5-ylamino)-thieno[3,2-b]pyridine-2-carbonyl]-piperazine-1-carboxylic acid tert-butyl ester with HCl gas as described in Example 64B. MS: 392 (MH+); HPLC Rf: 3.51 min.; HPLC purity: 93%.

Example 67

A. (+/-)-(3-Hydroxy-pyrrolidin-1-yl)-[7-chloro-thieno[3,2-b]pyridin-2-yl]-methanone

This compound was prepared from (+/-)-3-hydroxypyrrolidine and lithium 7-chloro-thieno[3,2-b]pyridine-2-carboxylate by a procedure analogous to Example 1B. MS: 283/285 (MH+); HPLC Rf: 3.44 min.; HPLC purity 91%.

B. (+/-)-(3-Methoxy-pyrrolidin-1-yl)-[7-chloro-thieno[3,2-b]pyridin-2-yl]-methanone

NaH (0.07 g, 1.3 mmol) was added to a solution of (+/-)-(3-hydroxy-pyrrolidin-1-yl)-[7-chloro-thieno[3,2-b]pyridin-2-yl]-methanone (0.25 g, 0.88 mmol) in DMF (10 mL), at 0 °C. The reaction mixture was allowed to stir for 20 min, and MeI (0.188 g, 1.33 mmol) was added dropwise. After 3 h the reaction was quenched with saturated aqueous KCN (10 mL). The

aqueous layer was extracted with CH_2Cl_2 (3 x 10 mL). The combined organic extracts were dried (Na_2SO_4), and the solvent was removed. Purification by flash chromatography on silica gel (CH_2Cl_2/MeOH 94:6) afforded the title compound as a white solid (0.13 g, 50%). MS: 297/299 (MH+); HPLC Rf: 4.11 min; HPLC purity: 93%.

C. (+/-)-(3-Methoxy-pyrrolidin-1-yl)-[7-(2-methyl-1H-indol-5-ylamino)-thieno[3,2-b]pyridin-2-yl]-methanone

The title compound was prepared from (3-methoxy-pyrrolidin-1-yl)-[7-chloro-thieno[3,2-b]pyridin-2-yl]-methanone and 2-methyl-1H-indol-5-ylamine by a procedure analogous to Example 1C. MS: 407 (MH+); HPLC Rf: 4.22 min.; HPLC purity 96%.

Example 68

(3R)-(3-Methoxy-pyrrolidin-1-yl)-[7-(2-methyl-1H-indol-5-ylamino)-thieno[3,2-b]pyridin-2-yl]-methanone

This compound was prepared by methods analogous to Example 67, using enantiomerically pure (3R)-3-hydroxy-pyrrolidine as a starting material. MS: 407 (MH+); HPLC Rf: 4.23 min.; HPLC purity: 98%.

Example 69

(3S)-(3-Methoxy-pyrrolidin-1-yl)-[7-(2-methyl-1H-indol-5-ylamino)-thieno[3,2-b]pyridin-2-yl]-methanone

This compound was prepared by methods analogous to Example 67, using enantiomerically pure (3S)-3-hydroxy-pyrrolidine as a starting material. MS: 407 (MH+); HPLC Rf: 4.21 min.; HPLC purity: 97%.

Example 70

A. (+/-)-[1-(7-Chloro-thieno[3,2-b]pyridine-2-carbonyl)-pyrrolidin-3-yl]-carbamic acid tert-butyl ester

The title compound was prepared from lithium 7-chloro-thieno[3,2-b]pyridine-2-carboxylate and (+/-)-pyrrolidin-3-yl-carbamic acid tert butyl ester by a method analogous to Example 1B. MS: 382/384 (MH+); HPLC Rf: 5.21 min.; HPLC purity 99%.

B. (+/-)-[1-[7-(2-Methyl-1H-indol-5-ylamino)-thieno[3,2-b]pyridine-2-carbonyl]-pyrrolidin-3-yl]-carbamic acid tert-butyl ester

The title compound was prepared from (+/-)-[1-(7-chloro-thieno[3,2-b]pyridine-2-carbonyl)-pyrrolidin-3-yl]-carbamic acid tert-butyl ester and 2-methyl-1H-indol-5-ylamine by a procedure analogous to Example 1C. MS: 492 (MH+); HPLC Rf: 5.23 min.; HPLC purity 96%.

C. (+/-)-3-Amino-pyrrolidin-1-yl)-[7-(2-methyl-1H-indol-5-ylamino)-thieno[3,2-b]pyridin-2-yl]-methanone

The title compound was prepared by treating (+/-)-[1-[7-(2-methyl-1H-indol-5-ylamino)-thieno[3,2-b]pyridine-2-carbonyl]-pyrrolidin-3-yl]-carbamic acid tert-butyl ester with HCl gas as described in Example 64B. MS: 392 (MH+); HPLC Rf: 3.30 min.; HPLC purity: 99%.

Example 71

A. (+/-)-Dimethylsulfamic acid {1-[7-chloro-thieno[3,2-b]pyridine-2-carbonyl]-pyrrolidin-3-yl}-amide

The title compound was prepared from dimethylsulfamoyl chloride and (3-amino-pyrrolidin-1-yl)-(7-chloro-thieno[3,2-b]pyridin-2yl)-methanone by a procedure analogous to Example 64C. MS: 389/391 (MH+); HPLC Rf: 4.26 min.; HPLC purity 99%.

B. (+/-)-Dimethylsulfamic acid {1-[7-(2-methyl-1H-indol-5-ylamino)-thieno[3,2-b]pyridine-2-carbonyl]-pyrrolidin-3-yl}-amide

The title compound was prepared from (+/-)-dimethylsulfamic acid {1-[7-chloro-thieno[3,2-b]pyridine-2-carbonyl]-pyrrolidin-3-yl}-amide and 2-methyl-1H-indol-5-ylamine by a procedure analogous to Example 1C. MS: 499 (MH+); HPLC Rf: 4.04 min.; HPLC purity 96%.

Example 72

A. (+/-)-Methanesulfonic acid {1-[7-chloro-thieno[3,2-b]pyridine-2-carbonyl]-pyrrolidin-3-yl}-amide

The title compound was prepared from methanesulfonyl chloride and (3-amino-pyrrolidin-1-yl)-(7-chloro-thieno[3,2-b]pyridin-2yl)-methanone by a procedure analogous to Example 64C. MS: 360/362 (MH+); HPLC Rf: 3.22 min.; HPLC purity 98%.

B. (+/-)-Methanesulfonic acid {1-[7-(2-methyl-1H-indol-5-ylamino)-thieno[3,2-b]pyridine-2-carbonyl]-pyrrolidin-3-yl}-amide

The title compound was prepared from (+/-)-methanesulfonic acid {1-[7-chloro-thieno[3,2-b]pyridine-2-carbonyl]-pyrrolidin-3-yl}-amide and 2-methyl-1H-indol-5-ylamine by a procedure analogous to Example 1C. MS: 470 (MH+); HPLC Rf: 3.23 min.; HPLC purity 93%.

Example 73

A. (+/-)-Cyclobutane carboxylic acid methyl-{1-[7-chloro-thieno[3,2-b]pyridine-2-carbonyl]-pyrrolidin-3-yl}-amide

The title compound was prepared from cyclobutane carbonyl chloride and (3-methylamino-pyrrolidin-1-yl)-(7-chloro-thieno[3,2-b]pyridin-2yl)-methanone by a procedure analogous to Example 64C. MS: 378/380 (MH+); HPLC Rf: 4.71 min.; HPLC purity 98%. .

B. (+/-)-Cyclobutane carboxylic acid methyl-{1-[7-(2-methyl-1H-indol-5-ylamino)-thieno[3,2-b]pyridine-2-carbonyl]-pyrrolidin-3-yl}-amide

The title compound was prepared from (+/-)-cyclobutane carboxylic acid methyl-{1-[7-chloro-thieno[3,2-b]pyridine-2-carbonyl]-pyrrolidin-3-yl}-amide and 2-methyl-1H-indol-5-ylamine by a procedure analogous to Example 1C. MS: 488 (MH+); HPLC Rf: 4.84 min.; HPLC purity 95%.

Example 74

A. (+/-)-Dimethylsulfamic acid methyl-{1-[7-chloro-thieno[3,2-b]pyridine-2-carbonyl]-pyrrolidin-3-yl}-amide

The title compound was prepared from dimethylsulfamoyl chloride and (3-methylamino-pyrrolidin-1-yl)-(7-chloro-thieno[3,2-b]pyridin-2yl)-methanone by a procedure analogous to Example 64C. MS: 403/405 (MH+); HPLC Rf: 4.76 min.; HPLC purity 98%.

B. (+/-)-Dimethylsulfamic acid methyl{1-[7-(2-methyl-1H-indol-5-ylamino)-thieno[3,2-b]pyridine-2-carbonyl]-pyrrolidin-3-yl}-amide

The title compound was prepared from (+/-)-dimethylsulfamic acid methyl-{1-[7-chloro-thieno[3,2-b]pyridine-2-carbonyl]-pyrrolidin-3-yl}-amide and 2-methyl-1H-indol-5-ylamine by a procedure analogous to Example 1C. MS: 513 (MH+); HPLC Rf: 4.76 min.; HPLC purity 92%.

Example 75

A. (+/-)-Methanesulfonic acid methyl-{1-[7-chloro-thieno[3,2-b]pyridine-2-carbonyl]-pyrrolidin-3-yl}-amide

The title compound was prepared from methanesulfonyl chloride and (3-methylamino-pyrrolidin-1-yl)-(7-chloro-thieno[3,2-b]pyridin-2yl)-methanone by a procedure analogous to Example 64C. MS: 374/376 (MH+); HPLC Rf: 4.14 min.; HPLC purity 98%.

B. (+/-)-Methanesulfonic acid methyl-{1-[7-(2-methyl-1H-indol-5-ylamino)-thieno[3,2-b]pyridine-2-carbonyl]-pyrrolidin-3-yl}-amide

The title compound was prepared from (+/-)-methanesulfonic acid methyl-{1-[7-chloro-thieno[3,2-b]pyridine-2-carbonyl]-pyrrolidin-3-yl}-amide and 2-methyl-1H-indol-5-ylamine by a procedure analogous to Example 1C. MS: 484 (MH+); HPLC Rf: 3.69 min.; HPLC purity 91%.

Example 76

A. (+/-)-7-Chloro-thieno[3,2-b]pyridine-2-carbonyl)-pyrrolidin-3-yl]-propionamide

The title compound was prepared from propionyl chloride and ((+/-)-3-amino-pyrrolidin-1-yl)-(7-chloro-thieno[3,2-b]pyridin-2yl)-methanone by a procedure analogous to Example 70A. MS: 340.0/338.0 (MH+); HPLC Rf: 3.675 min.; HPLC purity 98%.

B. (+/-)-{1-[7-(2-Methyl-1H-indol-5-ylamino)-thieno[3,2-b]pyridine-2-carbonyl]-pyrrolidin-3-yl}-propionamide

The title compound was prepared from (+/-)-7-chloro-thieno[3,2-b]pyridine-2-carbonyl)-pyrrolidin-3-yl]-propionamide and 2-methyl-1H-indol-5-ylamine by a procedure analogous to Example 1C. MS: 448.1 (MH+); HPLC Rf: 3.18 min.; HPLC purity: 94%.

Example 77

A. (3S)-(7-Chloro-thieno[3,2-b]pyridin-2-yl)-(3-ethoxy-pyrrolidin-1-yl)-methanone

The title compound was prepared from iodoethane and (3S)-(3-hydroxy-pyrrolidin-1-yl)-[7-chloro-thieno[3,2-b]pyridin-2-yl]-methanone by a procedure analogous to Example 67B. MS: 311.2/313.2 (MH+); HPLC Rf: 4.692 min.; HPLC purity: 96%.

B. (3S)-3-Ethoxy-pyrrolidin-1-yl)-[7-(2-methyl-1H-indol-5-ylamino)-thieno[3,2-b]pyridin-2-yl]-methanone

The title compound was prepared from (3S)-(7-chloro-thieno[3,2-b]pyridin-2-yl)-(3-ethoxy-pyrrolidin-1-yl)-methanone and 2-methyl-1H-indol-5-ylamine by a procedure analogous to Example 1C. MS: 421.3 (MH+); HPLC Rf: 4.786 min.; HPLC purity: 95%.

Example 78

A. (3R)-(7-Chloro-thieno[3,2-b]pyridin-2-yl)-(3-ethoxy-pyrrolidin-1-yl)-methanone

The title compound was prepared from iodoethane and (3R)-(3-hydroxy-pyrrolidin-1-yl)-[7-chloro-thieno[3,2-b]pyridin-2-yl]-methanone by a procedure analogous to Example 67B. MS: 311.2/313.2 (MH+); HPLC Rf: 4.697 min.; HPLC purity: 98%.

B. (3R)-3-Ethoxy-pyrrolidin-1-yl)-[7-(2-methyl-1H-indol-5-ylamino)-thieno[3,2-b]pyridin-2-yl]-methanone

The title compound was prepared from (3R)-(7-chloro-thieno[3,2-b]pyridin-2-yl)-(3-ethoxy-pyrrolidin-1-yl)-methanone and 2-methyl-1H-indol-5-ylamine by a procedure analogous to Example 1C. MS: 421.3 (MH+); HPLC Rf: 4.79 min.; HPLC purity: 97%.

Example 79

A. (3R)-(7-Chloro-thieno[3,2-b]pyridin-2-yl)-(3-cyclopropylmethoxy-pyrrolidin-1-yl)-methanone

The title compound was prepared from bromomethyl-cyclopropane and (3R)-(3-hydroxy-pyrrolidin-1-yl)-[7-chloro-thieno[3,2-b]pyridin-2-yl]-methanone by a procedure analogous to Example 67B. MS: 337.2/339.2 (MH+); HPLC Rf: 5.232 min.; HPLC purity 85%.

B. (3R)-(3-Cyclopropylmethoxy-pyrrolidin-1-yl)-[7-(2-methyl-1H-indol-5-ylamino)-thieno[3,2-b]pyridin-2-yl]-methanone

The title compound was prepared from (3R)-(7-chloro-thieno[3,2-b]pyridin-2-yl)-(3-cyclopropylmethoxy-pyrrolidin-1-yl)-methanone and 2-methyl-1H-indol-5-ylamine by a procedure analogous to Example 1C. MS: 447.2 (MH+); HPLC Rf: 5.341 min.; HPLC purity: 100%.

Example 80

A. (3S)-(7-Chloro-thieno[3,2-b]pyridin-2-yl)-(3-cyclopropylmethoxy-pyrrolidin-1-yl)-methanone

The title compound was prepared from bromomethyl-cyclopropane and (3S)-(3-hydroxy-pyrrolidin-1-yl)-[7-chloro-thieno[3,2-b]pyridin-2-yl]-methanone by a procedure analogous to Example 67B. MS: 337.2/339.2 (MH+); HPLC Rf: 5.232 min.; 85%.

B. (3S)-(3-Cyclopropylmethoxy-pyrrolidin-1-yl)-[7-(2-methyl-1H-indol-5-ylamino)-thieno[3,2-b]pyridin-2-yl]-methanone

The title compound was prepared from (3S)-(7-chloro-thieno[3,2-b]pyridin-2-yl)-(3-cyclopropylmethoxy-pyrrolidin-1-yl)-methanone and 2-methyl-1H-indol-5-ylamine by a procedure analogous to Example 1C. MS: 447.2 (MH+); HPLC Rf: 5.341 min.; HPLC purity: 100%.

Example 81

A. (3R)-(7-Chloro-thieno[3,2-b]pyridin-2-yl)-[3-(2-methoxy-ethoxy)-pyrrolidin-1-yl]-methanone

The title compound was prepared from 1-bromo-2-methoxy-ethane and (3R)-(3-hydroxy-pyrrolidin-1-yl)-[7-chloro-thieno[3,2-b]pyridin-2-yl]-methanone by a procedure analogous to Example 67B. MS: 341.2/343.2 (MH+); HPLC Rf: 4.082 min.; HPLC purity: 96%.

B. (3R)-[3-(2-Methoxy-ethoxy)-pyrrolidin-1-yl]-[7-(2-methyl-1H-indol-5-ylamino)-thieno[3,2-b]pyridin-2-yl]-methanone

The title compound was prepared from (3R)-(7-chloro-thieno[3,2-b]pyridin-2-yl)-[3-(2-methoxy-ethoxy)-pyrrolidin-1-yl]-methanone and 2-methyl-1H-indol-5-ylamine by a procedure analogous to Example 1C. MS: 451.3 (MH+); HPLC Rf: 4.385 min.; HPLC purity: 97%.

Example 82

A. (3S)-(7-Chloro-thieno[3,2-b]pyridin-2-yl)-[3-(2-methoxy-ethoxy)-pyrrolidin-1-yl]-methanone

The title compound was prepared from 1-bromo-2-methoxy-ethane and (3S)-(3-hydroxy-pyrrolidin-1-yl)-[7-chloro-thieno[3,2-b]pyridin-2-yl]-methanone by a procedure analogous to Example 67B. MS: 341.2/343.2 (MH+); HPLC Rf: 4.236 min.; HPLC purity: 77%.

B. (3S)-[3-(2-Methoxy-ethoxy)-pyrrolidin-1-yl]-[7-(2-methyl-1H-indol-5-ylamino)-thieno[3,2-b]pyridin-2-yl]-methanone

The title compound was prepared from (3S)-(7-chloro-thieno[3,2-b]pyridin-2-yl)-[3-(2-methoxy-ethoxy)-pyrrolidin-1-yl]-methanone and 2-methyl-1H-indol-5-ylamine by a procedure analogous to Example 1C. MS: 451.2 (MH+); HPLC Rf: 4.357 min.; HPLC purity: 97%.

Examples 83-88

Compounds from examples 83-88 were synthesized by one of two methods. Method A is a two-step method analogous to that described in Example 1B/C. Method B involves the coupling of an amine to 7-(2-methyl-1H-indol-5-ylamino)-thieno[3,2-b]pyridine-2-carboxylic acid by a method analogous to Example 21B.

Example Number	Compound Name	Method	MS (MH+)	HPLC Purity	HPLC Rf (min)
83	(+/-)-7-(2-Methyl-1H-indol-5-ylamino)-thieno[3,2-b]pyridine-2-carboxylic acid (1-benzyl-pyrrolidin-3-yl)-methyl-amide	B	496.2	n.d.	n.d.
84	(2S)-[7-(2-Methyl-1H-indol-5-ylamino)-thieno[3,2-b]pyridin-2-yl]-(2-pyrrolidin-1-ylmethyl-pyrrolidin-1-yl)-methanone	B	460.4	96	4.80
85	(2S)-(2-Benzhydryl-pyrrolidin-1-yl)-[7-(2-methyl-1H-indol-5-ylamino)-thieno[3,2-b]pyridin-2-yl]-methanone	B	543.4	96	6.86
86	(2S)-[7-(2-Methyl-1H-indol-5-ylamino)-thieno[3,2-b]pyridin-2-yl]-(2-phenylaminomethyl-pyrrolidin-1-yl)-methanone	B	482.2	98	5.78
87	(3R,4R)-(3,4-Dihydroxy-pyrrolidin-1-yl)-[7-(2-methyl-1H-indol-5-ylamino)-thieno[3,2-b]pyridin-2-yl]-methanone	B	409.2	97	3.42
88	(3R,4R)-(3,4-Dihydroxy-pyrrolidin-1-yl)-[7-(2-methyl-1H-indol-5-ylamino)-thieno[3,2-b]pyridin-2-yl]-methanone	B	409.2	97	3.41

Example 89

A. (3S,4S)-(7-Chloro-thieno[3,2-b]pyridin-2-yl)-(3,4-dihydroxy-pyrrolidin-1-yl)-methanone

The title compound was prepared from lithium 7-chloro-thieno[3,2-b]pyridine-2-carboxylate and (3S,4S)-pyrrolidine-3,4-diol by a procedure analogous to Example 1B. MS: 299.3/301.3 (MH+); HPLC Rf: 3.091 min.; HPLC purity: 99%.

B. (3S,4S)-(7-Chloro-thieno[3,2-b]pyridin-2-yl)-(3,4-dimethoxy-pyrrolidin-1-yl)-methanone

NaH (254 mg, 6.37 mmol) was added to a solution of (3S,4S)-(7-chloro-thieno[3,2-b]pyridin-2-yl)-(3,4-dihydroxy-pyrrolidin-1-yl)-methanone (543 mg, 1.82 mmol) in DMF at 0°C. After 30 min., MeI (645 mg, 4.55 mmol) was added dropwise. The resulting solution was allowed to warm to room temperature and stir for 12 h. The reaction was treated with saturated KCN (aq) and saturated ammonium chloride (aq). The aqueous layer was extracted with EtOAc (2x) the combined organic layers were dried over magnesium sulfate. The resulting material was purified on silica gel by flash column chromatography eluting with CH_2Cl_2/MeOH (98/2) to afford the title compound as a white solid (220 mg, 37%). MS: 327.2/329.2 (MH+); HPLC Rf: 4.448 min.; HPLC purity: 99%.

C. (3S,4S)-(3,4-Dimethoxy-pyrrolidin-1-yl)-[7-(2-methyl-1H-indol-5-ylamino)-thieno[3,2-b]pyridin-2-yl]-methanone

The title compound was prepared from (3S,4S)-(7-chloro-thieno[3,2-b]pyridin-2-yl)-(3,4-dimethoxy-pyrrolidin-1-yl)-methanone and 2-methyl-1H-indol-5-ylamine by a procedure analogous to Example 1C MS: 437.4 (MH+); HPLC Rf: 4.432 min.; HPLC purity: 98%.

Example 90

(3R,4R)-(3,4-Dimethoxy-pyrrolidin-1-yl)-[7-(2-methyl-1H-indol-5-ylamino)-thieno[3,2-b]pyridin-2-yl]-methanone

The title compound was prepared by a procedure analogous to Example 89 using (3R,4R)- pyrrolidine-3,4-diol as starting material. MS: 437.4 (MH+); HPLC Rf: 4.052 min.; HPLC purity: 98%.

Example 91

meso-(3,4-Dimethoxy-pyrrolidin-1-yl)-[7-(2-methyl-1H-indol-5-ylamino)-thieno[3,2-b]pyridin-2-yl]-methanone

The title compound was prepared by a procedure analogous to Example 89 using *meso*-pyrrolidine-3,4-diol as starting material. MS: 437.2 (MH+); HPLC Rf: 4.141 min.; HPLC purity: 97%.

Example 92

A. (S)-2-(1-Hydroxy-1-methyl-ethyl)-pyrrolidine-1-carboxylic acid benzyl ester

Methylmagnesium bromide (3.8 mL, 3.80 mmol, 3.0 M in Et_2O) was added dropwise to a solution of (S)-Pyrrolidine-1,2-dicarboxylic acid 1-benzyl ester 2-methyl ester (1.0 g, 3.8 mmol) in THF at 0°C. After 3 h the reaction was quenched with saturated NH_4Cl (aq), the aqueous layer was extracted with Et_2O (3X). The combined organic extracts were dried over Na_2SO_4, and the resulting material was purified on silica gel by flash column chromatography CH_2Cl_2/MeOH (97/3) to afford the title compound as a white solid (727 mg, 72%). MS: 264.2 (MH+); HPLC Rf: n.d.; HPLC purity: n.d.

B. (S)-2-Pyrrolidin-2-yl-propan-2-ol

A mixture of (S)-2-(1-hydroxy-1-methyl-ethyl)-pyrrolidine-1-carboxylic acid benzyl ester (0.727 g, 2.76 mmol) and Pd/C (10%, 72 mg) in EtOH was shaken with H_2 in a Parr bottle under 50 psi. After 12 h the reaction mixture was filtered through celite. HCl (9 mmol, 1 N in Et_2O) was added to the filtrate, the filtrate was then concentrated to give a white solid (350 mg, 98%).

C. (2S)-[2-(1-Hydroxy-1-methyl-ethyl)-pyrrolidin-1-yl]-[7-(2-methyl-1H-indol-5-ylamino)-thieno[3,2-b]pyridin-2-yl]-methanone

The title compound was prepared from 7-(2-methyl-1H-indol-5-ylamino)-thieno[3,2-b]pyridine-2-carboxylic acid and (S)-2-pyrrolidin-2-yl-propan-2-ol by a procedure analogous to Example 21B. MS: 435.3; HPLC Rf: 4.134 min.; HPLC purity 95%.

Example 93

A. (6-Amino-3-aza-bicyclo[3.1.0]hex-3-yl)-(7-chloro-thieno[3,2-b]pyridin-2-yl)-methanone

Trifluoroacetic acid (2mL) was added to a suspension of {3-[7-chloro-thieno[3,2-b]pyridine-2-carbonyl]-3-aza-bicyclo[3.1.0]hex-6-yl}-carbamic acid tert-butyl ester (1.43 g, 3.63 mmol) in CH_2Cl_2. After 24 h the reaction mixture was concentrated, and the resulting oil was purified on silica gel by flash column chromatography CH_2Cl_2/MeOH (80/20) to afford the title compound as a white solid (1.27 g, 99%). MS: 294.2/296.2 (MH+); HPLC Rf: 3.085 min.; HPLC purity: 97%.

B. (7-Chloro-thieno[3,2-b]pyridin-2-yl)-(6-dimethylamino-3-aza-bicyclo[3.1.0]hex-3-yl)-methanone

$NaBH_3CN$ (211 mg, 3.36 mmol) was added to a solution of (6-amino-3-aza-bicyclo[3.1.0]hex-3-yl)-(7-chloro-thieno[3,2-b]pyridin-2-yl)-methanone (250 mg, 0.85 mmol) and formaldehyde (1.14 mL, 17 mmol) in CH_3CN at 0°C. After 30 min AcOH (0.5 mL) was added and the reaction mixture was allowed to warm to room temperature. After 1 h the reaction mixture was concentrated, and the resulting residue was dissolved in H_2O. The resulting aqueous layer was adjusted to pH 9 with 6N NaOH. The resulting solution was extracted with CH_2Cl_2 (2X) and the combined organic xtracts were dried over Na_2SO_4, filtered, then concentrated. The resulting material was purified on silica gel by flash column chromatography

CH_2Cl_2/MeOH (85/15) to afford the title compound as a white solid (44 mg, 16%). MS: 322.2/324.2 (MH+); HPLC Rf: 3.62 min.; HPLC purity 95%.

C. (6-Amino-3-aza-bicyclo[3.1.0]hex-3-yl)-[7-(2-methyl-1H-indol-5-ylamino)-thieno[3,2-b]pyridin-2-yl]-methanone

The title compound was prepared from (7-chloro-thieno[3,2-b]pyridin-2-yl)-(6-dimethylamino-3-aza-bicyclo[3.1.0]hex-3-yl)-methanone and 2-methyl-1H-indol-5-ylamine by a procedure analogous to example 1C. MS: 432.2 (MH+); HPLC Rf: 4.346 min.; HPLC purity: 99%.

Example 94

A. (S)-2-Morpholin-4-ylmethyl-pyrrolidine-1-carboxylic acid tert-butyl ester

Methanesulfonyl chloride (1.7 g, 14.9 mmol) was added dropwise to a solution of (S)-2-hydroxymethyl-pyrrolidine-1-carboxylic acid tert-butyl ester (1.5 g, 7.45 mmol) and triethylamine (753 mg mg, 7.45 mmol) in CH_2Cl_2 at 0°C. After 3 h reaction mixture was concentrated to give a white solid. The resulting solid was suspended in toluene, morpholine (1.3 g, 14.9 mmol) was added, and the resulting mixture was heated to 110°C in a sealed tube. After 12 h the reaction mixture was concentrated, the resulting residue was dissolved in EtOAc and water, the layers were separated, and the aqueous was further extracted with EtOAc. The combined organic extracts were dried over Na_2SO_4, and the material was purified on silica gel by flash column chromatography CH_2Cl_2/MeOH/NH_4OH (98.5/1/0.5) to afford the title compound as a white solid (800 mg, 40%). MS: 271.2 (MH+); HPLC Rf: n.d.; HPLC purity: n.d.

B. (S)-4-Pyrrolidin-2-ylmethyl-morpholine

HCl (g) was introduced into a solution of (S)-2-morpholin-4-ylmethyl-pyrrolidine-1-carboxylic acid tert-butyl ester (400 mg, 1.47 mmol) in MeOH. After 5 min., the reaction solution was concentrated under reduced pressure to give a white solid (300 mg, 99%). MS: 170.9 (MH+); HPLC Rf: n.d.; HPLC purity: n.d.

C. (2S)-[7-(2-Methyl-1H-indol-5-ylamino)-thieno[3,2-b]pyridin-2-yl]-(2-morpholin-4-ylmethyl-pyrrolidin-1-yl)-methanone

The title compound was prepared from (S)-4-pyrrolidin-2-ylmethyl-morpholine and 7-(2-methyl-1H-indol-5-ylamino)-thieno[3,2-b]pyridine-2-carboxylic acid by a procedure analogous to Example 21B. MS: 476.3 (MH+); HPLC Rf: 5.378 min.; HPLC purity: 92%.

Compounds from examples 95-98 were synthesized by a procedure analogous to Example 94.

Example Number	Compound Name	MS (MH+)	HPLC purity	HPLC Rf (min)

95	(2R)-[7-(2-Methyl-1H-indol-5-ylamin)-thieno[3,2-b]pyridin-2-yl]-(2-morpholin-4-ylmethyl-pyrrolidin-1-yl)-methanone	476.1	92	5.52
96	(2S)-(2-Dimethylaminomethyl-pyrrolidin-1-yl)-[7-(2-methyl-1H-indol-5-ylamino)-thieno[3,2-b]pyridin-2-yl]-methanone	434.2	98	4.63
97	(2)-(2-Dimethylaminomethyl-pyrrolidin-1-yl)-[7-(2-methyl-1H-indol-5-ylamino)-thieno[3,2-b]pyridin-2-yl]-methanone	434.4	98	4.65
98	(2R)-[7-(2-Methyl-1H-indol-5-ylamino)-thieno[3,2-b]pyridin-2-yl]-(2-pyrrolidin-1-ylmethyl-pyrrolidin-1-yl)-methanone	460.1	n.d.	n.d.

Example 99

(3R)-[7-(2,3-Dimethyl-1H-indol-5-ylamino)-thieno[3,2-b]pyridin-2-yl]-(3-methoxy-pyrrolidin-1-yl)-methanone

A solution of (3R)-(7-chloro-thieno[3,2-b]pyridin-2-yl)-(3-methoxy-pyrrolidin-1-yl)-methanone (139 mg, 0.47 mmol) and 2,3-dimethyl-1H-indol-5-ylamine (75 mg, 0.47 mmol) in EtOH (10 mL) was heated to reflux. After 12 h the reaction mixture was concentrated onto silica gel (5 mL) and purified on silica gel by flash column chromatography CH_2Cl_2/MeOH/NH_4OH (98.5/1/0.5) to afford the title compound as a yellow solid, (190 mg). MS: 421.3 (MH+); HPLC Rf: 4.708 min.; HPLC purity: 99%.

Example 100

(3S)-[7-(2,3-Dimethyl-1H-indol-5-ylamino)-thieno[3,2-b]pyridin-2-yl]-(3-methoxy-pyrrolidin-1-yl)-methanone

The title compound was prepared from (3S)-(7-chloro-thieno[3,2-b]pyridin-2-yl)-(3-methoxy-pyrrolidin-1-yl)-methanone and 2,3-dimethyl-1H-indol-5-ylamine by a procedure analogous to Example 99. MS: 421.2 (MH+); HPLC Rf: 4.80 min.; HPLC purity: 99%.

Examples 101-102

Compounds from examples 101-102 were synthesized by a procedure analogous to that described in Example 1B/99A.

Example Number	Compound Name	MS (MH+)	HPLC purity	HPLC Rf (min)
101	(2R)-[7-(2,3-Dimethyl-1H-indol-5-ylamino)-			

	thieno[3,2-b]pyridin-2-yl]-(2-methoxymethyl-pyrrolidin-1-yl)-methanone	35	6%	.11
102	(2S)-[7-(2,3-Dimethyl-1H-indol-5-ylamino)-thieno[3,2-b]pyridin-2-yl]-(2-methoxymethyl-pyrrolidin-1-yl)-methanone	35	7%	.10

Example 103

(3R)-[7-(3-Chloro-2-methyl-1H-indol-5-ylamino)-thieno[3,2-b]pyridin-2-yl]-(3-methoxy-pyrrolidin-1-yl)-methanone

A solution of (3R)-(7-chloro-thieno[3,2-b]pyridin-2-yl)-(3-methoxy-pyrrolidin-1-yl)-methanone (75 mg, 0.25 mmol) and 3-chloro-2-methyl-1H-indol-5-ylamine (45 mg, 0.25 mmol) in EtOH (10 mL) was heated to reflux. After 48 h the reaction mixture was concentrated onto silica gel (5 mL) and purified on silica gel by flash column chromatography CH_2Cl_2/MeOH/NH_4OH (95/4/1) to afford the title compound as a yellow solid, (94 mg). MS: 441.2/443.2, 407.2 (MH+); HPLC Rf: 4.93 min.; HPLC purity: 98%.

Example 104

(3S)-[7-(3-Chloro-2-methyl-1H-indol-5-ylamino)-thieno[3,2-b]pyridin-2-yl]-(3-methoxy-pyrrolidin-1-yl)-methanone

The title compound was prepared from (3S)-(7-chloro-thieno[3,2-b]pyridin-2-yl)-(3-methoxy-pyrrolidin-1-yl)-methanone and 3-chloro-2-methyl-1H-indol-5-ylamine by a procedure analogous to Example 103. MS: 441.2/443.2; 407.2(MH+); HPLC Rf: 4.96 min.; HPLC purity: 98%.

Examples 105-106

Compounds from examples 105-106 were synthesized by a procedure analogous to that described in Examples 1B/103A.

105	(2R)-[7-(3-Chloro-2-methyl-1H-indol-5-ylamino)-thieno[3,2-b]pyridin-2-yl]-(2-methoxymethyl-pyrrolidin-1-yl)-methanone	457	99%	5.37
106	(2S)-[7-(3-Chloro-2-methyl-1H-indol-5-ylamino)-thieno[3,2-b]pyridin-2-yl]-(2-methoxymethyl-pyrrolidin-1-yl)-methanone	457	98%	5.37

Example 107

A. 1-(1-Benzhydryl-azetidin-3-yl)-pyrrolidine

Pyrrolidine (142 mg, 2 mmol) and tri thylamine (100 mg, 1 mmol) were added to a solution of methanesulfonic acid 1-benzhydryl-azetidin-3-yl ester (317.4mg, 1 mmol) in DMF

(6 mL). (The methanesulfonic acid 1-benzhydryl-azetidin-3-yl ester was prepared as described in *J. Org. Chem.* 1991, 56, 6729-6730). The reaction mixture was heated at 70 °C overnight. After cooling to room temperature, the reaction mixture was treated with water. The aqueous layer was extracted with EtOAc (3 X 15 mL). The combined organic extracts were washed with brine and dried over sodium sulfate. The solvent was then removed under reduced pressure. Purification by flash chromatography on silica gel (CH_2Cl_2/MeOH 96:4) afforded the title compound as an oil (184 mg, 65%). MS: 293 (MH+); HPLC Rf: 5.95 min; HPLC purity: 92%.

B. 1-Azetidin-3-yl-pyrrolidine

HCl (gas) was bubbled through a solution of 1-(1-benzhydryl-azetidin-3-yl)-pyrrolidine (184 mg, 0.63 mmol) in MeOH (10 mL). After 15 min, TLC showed the reaction to be complete. The resulting HCl salt was obtained as a light yellow solid after removal of the solvent. The HCl salt was then re-dissolved in MeOH and exposed to hydrogen in presence of $Pd(OH)_2$ (53 mg) for 4 hours. The $Pd(OH)_2$ was removed by filtration through Celite and was washed with MeOH. The titled compound was afforded as a light yellow solid (105 mg, 92%) after concentrating the filtrate under reduced pressure. MS: 363 (MH+)

C. [7-(2-Methyl-1H-indol-5-ylamino)-thieno[3,2-b]pyridin-2-yl]-(3-pyrrolidin-1-yl-azetidin-1-yl)-methanone

The title compound was prepared from 1-azetidin-3-yl-pyrrolidine and 7-(2-methyl-1H-indol-5-ylamino)-thieno[3,2-b]pyridine-2-carboxylic acid by a procedure analogous to Example 21B. MS: 312 (MH+); HPLC Rf: 3.211 min; HPLC purity: 96%.

Example 108-110

Compounds from examples 108-110 were synthesized by the same method described for Example 107.

Example Number	Compound Name	MS (MH+)	HPLC Purity	HPLC Rf (min)
108	(3-Dimethylamino-azetidin-1-yl)-[7-(2-methyl-1H-indol-5-ylamino)-thieno[3,2-b]pyridin-2-yl]-methanone	406	96%	3.22
109	(3-Diethylamino-azetidin-1-yl)-[7-(2-methyl-1H-indol-5-ylamino)-thieno[3,2-b]pyridin-2-yl]-methanone	434	94%	4.30
110	[7-(2-Methyl-1H-indol-5-ylamino)-thieno[3,2-b]pyridin-2-yl]-(3-morpholin-4-yl-azetidin-1-yl)-methanone	448	97%	4.09

Example 111

A. 4-(7-Chloro-thieno[3,2-b]pyridine-2-carbonyl)-piperazine-1-carboxylic acid tert-butyl ester

The title compound was prepared from lithium 7-chloro-thieno[3,2-b]pyridine-2-carboxylate and piperazine-1-carboxylic acid tert-butyl ester by a procedure analogous to Example 1B. MS: 383 (MH+); HPLC Rf: 5.69; HPLC purity: 99%.

B. 1-[4-(7-Chloro-thieno[3,2-b]pyridine-2-carbonyl)-piperazin-1-yl]-ethanone

HCl (gas) was bubbled through a solution of 4-(7-chloro-thieno[3,2-b]pyridine-2-carbonyl)-piperazine-1-carboxylic acid tert-butyl ester (270 mg, 0.71 mmol) in MeOH (5 mL). After 15 min, TLC showed the reaction to be complete. The resulting HCl salt was obtained as a yellow oil (199 mg, 99%) after the solvent was removed under pressure. The title compound was prepared from the resulting HCl salt and acetyl chloride by a procedure analogous to Example 70A. MS: 325 (MH+); HPLC Rf: 3.62; HPLC purity: 95%.

C. 1-{4-[7-(2-Methyl-1H-indol-5-ylamino)-thieno[3,2-b]pyridine-2-carbonyl]-piperazin-1-yl}-ethanone

The title compound was prepared from 1-[4-(7-chloro-thieno[3,2-b]pyridine-2-carbonyl)-piperazin-1-yl]-ethanone and 2-methyl-1H-indol-5-ylamine by a procedure analogous to Example 1C. MS: 434 (MH+); HPLC Rf: 3.52; HPLC purity: 99%.

Examples 112-113

Compounds from examples 112-113 were synthesized by the same method as described for Example 111. In each case, 4-(7-chloro-thieno[3,2-b]pyridine-2-carbonyl)-piperazine-1-carboxylic acid tert-butyl ester was treated with HCl (gas). The resulting HCl salt was treated with a commercially available sulfonyl chloride by a procedure analogous to Example 64B to give the corresponding sulfonamide. The sulfonamides were then coupled with 2-methyl-1H-indole-5-ylamine according to Example 1C to give the title compounds.

Example Number	Compound Name	MS (MH+)	HPLC Purity	HPLC Rf (min)
112	(4-Methanesulfonyl-piperazin-1-yl)-[7-(2-methyl-1H-indol-5-ylamino)-thieno[3,2-b]pyridin-2-yl]-methanone	470	98%	4.26
113	4-[7-(2-Methyl-1H-indol-5-ylamino)-thieno[3,2-b]pyridine-2-carbonyl]-piperazine-1-sulfonic acid dimethylamide	499	94%	4.76

Example 114

A. 1-Benzhydryl-azetidin-3-ylamine

Ammonia gas was bubbled through a solution of methanesulfonic acid 1-benzhydryl-azetidin-3-yl ester (952.4 mg, 3 mmol) in MeOH (15 mL). After 2 hours , TLC showed the reaction to be complete. The title compound was obtained as a white solid (643.5 mg, 90%) after removal of the solvent. MS: 239 (MH+); HPLC Rf: 3.54 min; HPLC purity: 98%.

B. N-(1-Benzhydryl-azetidin-3-yl)-acetamide

The title compound was prepared from 1-benzhydryl-azetidin-3-ylamine and acetyl chloride by a procedure analogous to Example 70A. MS: 281 (MH+); HPLC Rf: 5.57 min; HPLC purity: 93%.

C. N-Azetidin-3-yl-acetamide

The title compound was prepared by a method analogous to Example 70A. MS: 115 (MH+).

D. N-{1-[7-(2-Methyl-1H-indol-5-ylamino)-thieno[3,2-b]pyridine-2-carbonyl]-azetidin-3-yl}-acetamide

The title compound was prepared by a method analogous to Example 21B. MS: 421 (MH+); HPLC Rf: 4.43 min; HPLC purity: 95%.

Example 115

A. (7-Chloro-thieno[3,2-b]pyridin-2-yl)-(2R)-(2-ethoxymethyl-pyrrolidin-1-yl)-methanone

NaH (80 mg, 2 mmol) was added to a solution of (2R)-(2-hydroxymethyl-pyrrolidin-1-yl)-[7-chloro-thieno[3,2-b]pyridin-2-yl]-methanone (297 mg, 1 mmol) in DMF (5 mL), at 0 °C. The reaction mixture was allowed to stir for 20 min, and EtI (234 mg, 1.5 mmol) was added dropwise. After 3 h the reaction was quenched with saturated aqueous KCN (10 mL). The aqueous layer was extracted with CH_2Cl_2 (3 X 15 mL). The combined organic extracts were dried (Na_2SO_4), and the solvent was removed. Purification by flash chromatography on silica gel (CH_2Cl_2/MeOH 94:6) afforded the title compound as a white solid (145 mg, 50%). MS: 326 (MH+); HPLC Rf: 5.11 min; HPLC purity: 97%.

B. (2R)-(2-Ethoxymethyl-pyrrolidin-1-yl)-[7-(2-methyl-1H-indol-5-ylamino)-thieno[3,2-b]pyridin-2-yl]-methanone

A solution of (7-chloro-thieno[3,2-b]pyridin-2-yl)-pyrrolidin-1-yl-methanone (130 mg, 0.4 mmol) and 2-methyl-1H-indol-5-ylamine (70 mg, 0.48 mmol) in EtOH (5 mL) was heated to reflux for 48 h. The reaction mixture was cooled to room temperature and concentrated onto silica gel. Purification by flash chromatography on silica gel eluting with

CH_2Cl_2/MeOH/NEt_3 (94.5/5/0.5) afforded the title compound as a yellow solid (150 mg, 86%). MS: 435 (MH+); HPLC Rf: 5.37 min; HPLC purity: 98%.

Examples 116-122

Compounds from examples 116-122 were synthesized by the same method described for Example 115. In each case, a commercially available alkyl iodide was coupled with of 3R or 3S-(3-hydroxy-pyrrolidin-1-yl)-[7-chloro-thieno[3,2-b]pyridin-2-yl]-methanone by a procedure analogous to Example 115, and the resulting thienopyridine chloride were treated with 2-methyl-1H-indole-5-ylamine according to Example 1C to give the title compounds.

Example Number	Compound Name	MS (MH+)	HPLC Purity	HPLC Rf (min)
116	(2R)-(2-Isopropoxymethyl-pyrrolidin-1-yl)-[7-(2-methyl-1H-indol-5-ylamino)-thieno[3,2-b]pyridin-2-yl]-methanone	449	95%	6.14
117	(2S)-(2-Cyclopropylmethoxymethyl-pyrrolidin-1-yl)-[7-(2-methyl-1H-indol-5-ylamino)-thieno[3,2-b]pyridin-2-yl]-methanone	461	97%	5.68
118	(2R)-(2-Cyclopropylmethoxymethyl-pyrrolidin-1-yl)-[7-(2-methyl-1H-indol-5-ylamino)-thieno[3,2-b]pyridin-2-yl]-methanone	461	97%	5.69
119	[2-(2R)-(2-Methoxy-ethoxymethyl)-pyrrolidin-1-yl]-[7-(2-methyl-1H-indol-5-ylamino)-thieno[3,2-b]pyridin-2-yl]-methanone	466	96%	4.78
120	(2S)-(2-Ethoxymethyl-pyrrolidin-1-yl)-[7-(2-methyl-1H-indol-5-ylamino)-thieno[3,2-b]pyridin-2-yl]-methanone	435	96%	5.10
121	[2-(2S)-(2-Methoxy-ethoxymethyl)-pyrrolidin-1-yl]-[7-(2-methyl-1H-indol-5-ylamino)-thieno[3,2-b]pyridin-2-yl]-methanone	466	96%	4.58
122	(2S)-(2-Isopropoxymethyl-pyrrolidin-1-yl)-[7-(2-methyl-1H-indol-5-ylamino)-thieno[3,2-b]pyridin-2-yl]-methanone	450	95%	5.24

Exampl 123

A. (2S)-(7-Chloro-thieno[3,2-b]pyridin-2-yl)-(2-methoxymethyl-pyrrolidin-1-yl)-methanone

This compound was prepared as described for Example 1B, using (2S)-2-methoxymethylpyrrolidine as starting material.

B. (2S)-(2-Methoxymethyl-pyrrolidin-1-yl)-[7-(2-methyl-quinolin-6ylamino)-thieno[3,2-b]pyridin-2-yl]-methanone

Cesium Carbonate (117mg, 0.36 mmol) was added to a solution of (7-chloro-thieno[3,2-b]pyridin-2-yl)-(2-hydroxymethyl-pyrrolidin-1-yl)-methanone I(56 mg, .18 mmol) in DMF (4 mL). The reaction mixture was heated to 85 °C for 1.5 hours with stirring. After cooling to room temperature, 2-methyl-quinolin-6-ylamine (57 mg, 0.36 mmol) was added to the reaction mixture, and the resulting mixture was heated to 90 °C for 48 hours. The reaction mixture was treated with water and extracted with EtOAc (3 X 15 mL). The combined organic extracts were was dried over sodium sulfate, and the solvent was removed under reduced pressure. Purification by flash chromatography on silica gel with CH_2Cl_2/MeOH (95/5) afforded the title compound as a white solid. MS: 435 (MH+); HPLC Rf: 5.35 min; HPLC purity: 97%.

Example 124

(2R)-(2-Methoxymethyl-pyrrolidin-1-yl)-[7-(2-methyl-quinolin-6-ylamino)-thieno[3,2-b]pyridin-2-yl]-methanone

The title compound was prepared by method analogous to Example 123, using (2R)-2-methoxymethyl-pyrrolidine as a starting material. MS: 435 (MH+); HPLC Rf: 5.34 min; HPLC purity: 98%.

Example 125

A. (2R)-(2-Methoxymethyl-pyrrolidin-1-yl)-[7-(2-methyl-1H-indol-5-ylamino)-thieno[3,2-b]pyridin-2-yl]-methanone

This compound was prepared by method analogous to Example 1, using (2R)-2-methoxymethyl-pyrrolidine as a starting material.

B. N-(1-Acetyl-2-methyl-1H-indol-5-yl)-N-[2-(2R)-(2-methoxymethyl-pyrrolidine-1-carbonyl)-thieno[3,2-b]pyridin-7-yl]-acetamide

The title compound was prepared by method analogous to Example 70A using (2R)-(2-methoxymethyl-pyrrolidin-1-yl)-[7-(2-methyl-1H-indol-5-ylamino)-thieno[3,2-b]pyridin-2-yl]-methanone and acetyl chloride as starting materials. MS: 505 (MH+); HPLC Rf: 4.11 min; HPLC purity: 99%.

Example 126

A. (2R)-(2-Methoxymethyl-pyrrolidin-1-yl)-[7-(2-methyl-1H-indol-5-ylamino)-thieno[3,2-b]pyridin-2-yl]-methanone

This compound was prepared by method analogous to Example 1, using enantiomerically pure (2R)-2-methoxymethyl-pyrrolidine as a starting material.

B. 1-{5-[2-(2R)-(2-Methoxymethyl-pyrrolidine-1-carbonyl)-thieno[3,2-b]pyridin-7-ylamino]-2-methyl-indol-1-yl}-ethanone

The title compound was prepared by method analogous to Example 70A using (2R)-(2-methoxymethyl-pyrrolidin-1-yl)-[7-(2-methyl-1H-indol-5-ylamino)-thieno[3,2-b]pyridin-2-yl]-methanone and acetyl chloride as starting materials. MS: 463 (MH+); HPLC Rf: 4.88 min; HPLC purity: 94%.

Example 127

A. (2R)-(2-Methoxymethyl-pyrrolidin-1-yl)-[7-(2-methyl-1H-indol-5-ylamino)-thieno[3,2-b]pyridin-2-yl]-methanone

This compound was prepared by method analogous to Example 1, using enantiomerically pure (2R)-2-methoxymethyl-pyrrolidine as a starting material.

B. {7-[Ethyl-(1-ethyl-2-methyl-1H-indol-5-yl)-amino]-thieno[3,2-b]pyridin-2-yl}-(2R)-2-methoxymethyl-pyrrolidin-1-yl)-methanone

The title compound was prepared from (2R)-2-methoxymethyl-pyrrolidin-1-yl)-[7-(2-methyl-1H-indol-5-ylamino)-thieno[3,2-b]pyridin-2-yl]-methanone and EtI by a procedure analogous to Example 115A. MS: 449 (MH+); HPLC Rf: 5.53 min; HPLC purity: 95%.

Example 128

{7-[(1,2-Dimethyl-1H-indol-5-yl)-methyl-amino]-thieno[3,2-b]pyridin-2-yl}-(2R)-(2-methoxymethyl-pyrrolidin-1-yl)-methanone

The title compound was prepared by method analogous to Example 127, using MeI as the alkylating agent. MS: 435 (MH+); HPLC Rf: 5.38 min; HPLC purity: 97%.

Example 129

A. (R)-2-(1-Benzyl-pyrrolidin-2-yl)-propan-2-ol

The title compound was prepared from (R)-1-benzyl-pyrrolidine-2-carboxylic acid ethyl ester by a procedure analogous to Example 92A. MS: 220.2 (MH+); HPLC Rf: 2.247 min.; HPLC purity: 80%.

B. (R)-2-Pyrrolidin-2-yl-propan-2-ol

A mixture of (R)-2-(1-benzyl-pyrrolidin-2-yl)-propan-2-ol (582 mg, 2.65 mmol), HOAc (3 mL), and $Pd(OH)_2/C$ (200 mg) in MeOH was shaken in a Parr bottle with H_2 under 50 psi for 24 h. The reaction mixture was then filt red through celit eluting with MeOH. HCl (g) was passed through

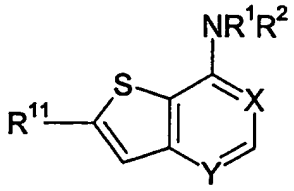
the filtrate, and the filtrat was then concentrated to afford the title compound as a gray solid (419 mg, 95%). MS: 130.1 (MH+); HPLC Rf: n.d.; HPLC purity: n.d.

C. (2R)-[2-(1-Hydroxy-1-methyl-ethyl)-pyrrolidin-1-yl]-[7-(2-methyl-1H-indol-5-ylamino)-thieno[3,2-b]pyridin-2-yl]-methanone

The title compound was prepared from 7-(2-methyl-1H-indol-5-ylamino)-thieno[3,2-b]pyridine-2-carboxylic acid and (R)-2-pyrrolidin-2-yl-propan-2-ol by a procedure analogous to Example 21B. MS: 435.2; HPLC Rf: 4.656 min.; HPLC purity: 97%.

CLAIMS

1. A compound of the formula of formula 1



1

or a pharmaceutically acceptable salt, prodrug or hydrate thereof,

X is N, CH or C(CN);

Y is N, CH, CF, or N→0;

R^1 is H or C_1-C_6 alkyl;

R^2 is 5 to 13 membered heterocyclic, wherein said R^2 group is optionally substituted by 1 to 5 R^5 substituents,

each R^5 is independently selected from halo, cyano, trifluoromethoxy, trifluoromethyl, $-C(O)R^8$, $-NR^6C(O)R^7$, $-C(O)NR^6R^7$, $-NR^6R^7$, $-OR^9$, $-SO_2NR^6R^7$, $-SO_2R^6$, $-NR^6SO_2R^7$, $-NR^6SO_2NR^9R^{10}$, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, $-(CH_2)_jO(CH_2)_qNR^6R^7$, $-(CH_2)_tO(CH_2)_qOR^9$, $-(CH_2)_tOR^9$, $-S(O)_j(C_1$-C_6 alkyl), $-(CH_2)_t(C_6$-C_{10} aryl), $-(CH_2)_t$(5 to 10 membered heterocyclic), $-(CH_2)_tO(CH_2)_q$(5 to 10 membered heterocyclic), $-C(O)(CH_2)_t$(5 to 10 membered heterocyclic), $-(CH_2)_jNR^7(CH_2)_qNR^6R^7$, $-(CH_2)_jNR^7CH_2C(O)NR^6R^7$, $-(CH_2)_jNR^7(CH_2)_qNR^9C(O)R^8$, $-(CH_2)_jNR^7(CH_2)_tO(CH_2)_qOR^9$, $-(CH_2)_jNR^7(CH_2)_qS(O)_j(C_1$-$C_6$ alkyl), $-(CH_2)_jNR^7(CH_2)_tR^6$, $-SO_2(CH_2)_t(C_6$-C_{10} aryl), and $-SO_2(CH_2)_t$(5 to 10 membered heterocyclic), wherein j is an integer from 0 to 2, t is an integer from 0 to 6, q is an integer from 2 to 6, the $-(CH_2)_q$- and $-(CH_2)_t$- moieties of the foregoing R^5 groups optionally include a carbon-carbon double or triple bond where t is an integer from 2 to 6, and the alkyl, aryl and heterocyclic moieties of the foregoing R^5 groups are optionally substituted by 1 to 3 substituents independently selected from halo, cyano, trifluoromethyl, $-C(O)R^8$, $-NR^6C(O)R^7$, $-C(O)NR^6R^7$, $-(CH_2)_tNR^6R^7$, $-SO_2R^6$, $-SO_2NR^6R^7$, C_1-C_6 alkyl, $-(CH_2)_t$(5 to 10 membered heterocyclic), $-(CH_2)_tO(CH_2)_qOR^9$, and $-(CH_2)_tOR^9$, wherein t is an integer from 0 to 6 and q is an integer from 2 to 6;

each R^6 and R^7 is independently selected from H, C_1-C_6 alkyl, $-(CH_2)_t(C_6$-C_{10} aryl), $-(CH_2)_t$(5 to 10 membered heterocyclic), $-(CH_2)_tO(CH_2)_qOR^9$, and $-(CH_2)_tOR^9$, wherein t is an integer from 0 to 6 and q is an integer from 2 to 6, and the alkyl, aryl and heterocyclic moieties of the foregoing R^6 and R^7 groups are optionally substituted by 1 to 3 substituents independently selected from halo, cyano, trifluoromethyl, $-C(O)R^8$, $-NR^9C(O)R^{10}$, $-C(O)NR^9R^{10}$, $-NR^9R^{10}$, C_1-C_6 alkyl, $-(CH_2)_t(C_6$-C_{10} aryl), $-(CH_2)_t$(5 to 10 membered

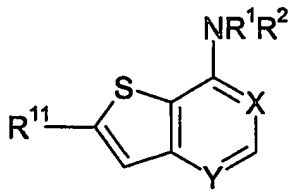
heterocyclic), $-(CH_2)_tO(CH_2)_qOR^9$, and $-(CH_2)_tOR^9$, wherein t is an integer from 0 to 6 and q is an integer from 2 to 6, with the proviso that where R^6 and R^7 are both attached to the same nitrogen, then R^6 and R^7 are not both bonded to the nitrogen directly through an oxygen;

each R^8 is independently selected from H, C_1-C_{10} alkyl, $-(CH_2)_t(C_6$-C_{10} aryl), and $-(CH_2)_t$(5 to 10 membered heterocyclic), wherein t is an integer from 0 to 6;

each R^9 and R^{10} is independently selected from H and C_1-C_6 alkyl;

R^{11} is $-C(O)NR^{12}R^{13}$, $-(CH_2)_tNR^{12}R^{13}$, $-NR^{12}C(=O)R^{13}$, $-SO_2R^{12}$, $-SO_2NR^{12}R^{13}$, $-NR^9SO_2R^{12}$, $-NR^9SO_2NR^{12}R^{13}$, $-C(=N\text{-}OR^{12})R^{13}$, $-C(=NR^{12})R^{13}$, $-NR^9C(=NR^{12})R^{13}$, $-C(=NR^{12})NR^9R^{13}$, $-NR^9C(=NR^{12})NR^9R^{13}$, $-C(O)R^{12}$ and $-CO_2R^{12}$ and wherein each R^{12} and R^{13} is independently selected from H, C_1-C_6 alkyl, $-(CH_2)_t(C_3$-C_{10} cycloalkyl), $-(CH_2)_t(C_6$-C_{10} aryl), $-(CH_2)_t$(5 to 10 membered heterocyclic), $-(CH_2)_tO(CH_2)_qOR^9$, $-(CH_2)_tOR^9$, wherein t is an integer from 0 to 6 and q is an integer from 2 to 6, and the alkyl, aryl and heterocyclic moieties of the foregoing R^{12} and R^{13} groups are optionally substituted by 1 to 3 substituents independently selected from R^5 or R^{12} and R^{13} taken together with the nitrogen to which they are attached to form a C_5-C_9 azabicyclic, aziridinyl, azetidinyl, pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl, thiomorpholinyl, isoquinolinyl, or dihydroisoquinolinyl ring, wherein said C_5-C_9 azabicyclic, aziridinyl, azetidinyl, pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl, thiomorpholinyl, isoquinolinyl, or dihydroisoquinolinyl ring are optionally substituted by 1 to 5 R^5 substituents, with the proviso R^{12} and R^{13} are not both bonded to the nitrogen directly through an oxygen.

2. A method of preparing a compound of the formula 1



1

or a pharmaceutically acceptable salt, prodrug or hydrate thereof,

X is N, CH or C(CN);

Y is N, CH, CF, or N→0;

R^1 is H or C_1-C_6 alkyl;

R^2 is 5 to 13 membered heterocyclic, wherein said R^2 group is optionally substituted by 1 to 5 R^5 substituents,

each R^5 is independently selected from halo, cyano, trifluoromethoxy, trifluoromethyl, $-C(O)R^8$, $-NR^6C(O)R^7$, $-C(O)NR^6R^7$, $-NR^6R^7$, $-OR^9$, $-SO_2NR^6R^7$, $-SO_2R^6$, $-NR^6SO_2R^7$, $-NR^6SO_2NR^9R^{10}$, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, $-(CH_2)_jO(CH_2)_qNR^6R^7$,

$-(CH_2)_tO(CH_2)_qOR^9$, $-(CH_2)_tOR^9$, $-S(O)_j(C_1-C_6$ alkyl), $-(CH_2)_t(C_6-C_{10}$ aryl), $-(CH_2)_t$(5 to 10 membered heterocyclic), $-(CH_2)_tO(CH_2)_q$(5 to 10 membered heterocyclic), $-C(O)(CH_2)_t$(5 to 10 membered heterocyclic), $-(CH_2)_jNR^7(CH_2)_qNR^6R^7$, $-(CH_2)_jNR^7CH_2C(O)NR^6R^7$, $-(CH_2)_jNR^7(CH_2)_qNR^9C(O)R^8$, $-(CH_2)_jNR^7(CH_2)_tO(CH_2)_qOR^9$, $-(CH_2)_jNR^7(CH_2)_qS(O)_j(C_1-C_6$ alkyl), $-(CH_2)_jNR^7(CH_2)_tR^6$, $-SO_2(CH_2)_t(C_6-C_{10}$ aryl), and $-SO_2(CH_2)_t$(5 to 10 membered heterocyclic), wherein j is an integer from 0 to 2, t is an integer from 0 to 6, q is an integer from 2 to 6, the $-(CH_2)_q-$ and $-(CH_2)_t-$ moieties of the foregoing R^5 groups optionally include a carbon-carbon double or triple bond where t is an integer from 2 to 6, and the alkyl, aryl and heterocyclic moieties of the foregoing R^5 groups are optionally substituted by 1 to 3 substituents independently selected from halo, cyano, trifluoromethyl, $-C(O)R^8$, $-NR^6C(O)R^7$, $-C(O)NR^6R^7$, $-(CH_2)_tNR^6R^7$, $-SO_2R^6$, $-SO_2NR^6R^7$, C_1-C_6 alkyl, $-(CH_2)_t$(5 to 10 membered heterocyclic), $-(CH_2)_tO(CH_2)_qOR^9$, and $-(CH_2)_tOR^9$, wherein t is an integer from 0 to 6 and q is an integer from 2 to 6;

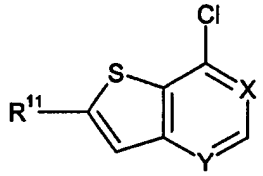
each R^6 and R^7 is independently selected from H, C_1-C_6 alkyl, $-(CH_2)_t(C_6-C_{10}$ aryl), $-(CH_2)_t$(5 to 10 membered heterocyclic), $-(CH_2)_tO(CH_2)_qOR^9$, and $-(CH_2)_tOR^9$, wherein t is an integer from 0 to 6 and q is an integer from 2 to 6, and the alkyl, aryl and heterocyclic moieties of the foregoing R^6 and R^7 groups are optionally substituted by 1 to 3 substituents independently selected from halo, cyano, trifluoromethyl, $-C(O)R^8$, $-NR^9C(O)R^{10}$, $-C(O)NR^9R^{10}$, $-NR^9R^{10}$, C_1-C_6 alkyl, $-(CH_2)_t(C_6-C_{10}$ aryl), $-(CH_2)_t$(5 to 10 membered heterocyclic), $-(CH_2)_tO(CH_2)_qOR^9$, and $-(CH_2)_tOR^9$, wherein t is an integer from 0 to 6 and q is an integer from 2 to 6, with the proviso that where R^6 and R^7 are both attached to the same nitrogen, then R^6 and R^7 are not both bonded to the nitrogen directly through an oxygen;

each R^8 is independently selected from H, C_1-C_{10} alkyl, $-(CH_2)_t(C_6-C_{10}$ aryl), and $-(CH_2)_t$(5 to 10 membered heterocyclic), wherein t is an integer from 0 to 6;

each R^9 and R^{10} is independently selected from H and C_1-C_6 alkyl;

R^{11} is $-C(O)NR^{12}R^{13}$, $-(CH_2)_tNR^{12}R^{13}$, $-NR^{12}C(=O)R^{13}$, $-SO_2R^{12}$, $-SO_2NR^{12}R^{13}$, $-NR^9SO_2R^{12}$, $-NR^9SO_2NR^{12}R^{13}$, $-C(=N-OR^{12})R^{13}$, $-C(=NR^{12})R^{13}$, $-NR^9C(=NR^{12})R^{13}$, $-C(=NR^{12})NR^9R^{13}$, $-NR^9C(=NR^{12})NR^9R^{13}$, $-C(O)R^{12}$ and $-CO_2R^{12}$ and wherein each R^{12} and R^{13} is independently selected from H, C_1-C_6 alkyl, $-(CH_2)_t(C_3-C_{10}$ cycloalkyl), $-(CH_2)_t(C_6-C_{10}$ aryl), $-(CH_2)_t$(5 to 10 membered heterocyclic), $-(CH_2)_tO(CH_2)_qOR^9$, $-(CH_2)_tOR^9$, wherein t is an integer from 0 to 6 and q is an integer from 2 to 6, and the alkyl, aryl and heterocyclic moieties of the foregoing R^{12} and R^{13} groups are optionally substituted by 1 to 3 substituents independently selected from R^5 or R^{12} and R^{13} taken together with the nitrogen to which they are attached to form a C_5-C_9 azabicyclic, aziridinyl, az tidinyl, pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl, thiomorpholinyl, isoquinolinyl, or dihydroisoquinolinyl ring, wherein said C_5-C_9 azabicyclic, aziridinyl, azetidinyl, pyrrolidinyl, pip ridinyl, piperazinyl, morpholinyl,

thiomorpholinyl, isoquinolinyl, or dihydroisoquinolinyl ring are optionally substituted by 1 to 5 R^5 substituents, with the proviso R^{12} and R^{13} are not both bonded to the nitrogen directly through an oxygen, which comprises treating a compound of formula 22



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with HNR^1R^2 wherein X, Y, R^1, R^2, and R^{11} are as defined above.

3. The method of claim 2, wherein Y is N.

4. The compound of claim 1, wherein R^{11} is $-C(O)NR^{12}R^{13}$, $-SO_2R^{12}$, $-SO_2NR^{12}R^{13}$, $-C(=N-OR^{12})R^{13}$, and $-C(=NR^{12})R^{13}$ wherein each R^{12} and R^{13} is independently selected from H, C_1-C_6 alkyl, $-(CH_2)_tOR^9$, wherein t is an integer from 0 to 6, and the alkyl moiety of the foregoing R^{12} and R^{13} groups is optionally substituted by 1 to 3 substituents independently selected from halo, cyano, trifluoromethyl, $-C(O)R^8$, $-NR^9C(O)R^{10}$, $-C(O)NR^9R^{10}$, $-NR^9R^{10}$, C_1-C_6 alkyl, $-(CH_2)_t(C_6$-C_{10} aryl), $-(CH_2)_t$(5 to 10 membered heterocyclic), $-(CH_2)_tO(CH_2)_qOR^9$, and $-(CH_2)_tOR^9$, wherein t is an integer from 0 to 6 and q is an integer from 2 to 6, or R^{12} and R^{13} may be taken together with the nitrogen to which they are attached to form a C_5-C_9 azabicyclic, aziridinyl, azetidinyl, pyrrolidinyl, piperidinyl, piperazinyl, or morpholinyl ring wherein said C_5-C_9 azabicyclic, aziridinyl, azetidinyl, pyrrolidinyl, piperidinyl, piperazinyl, or morpholinyl ring are optionally substituted by 1 to 5 R^5 substituents, with the proviso R^{12} and R^{13} are not both bonded to the nitrogen directly through an oxygen.

5. The compound of claim 4, wherein R^{11} is $-C(O)NR^{12}R^{13}$, wherein each R^{12} and R^{13} is independently selected from H, C_1-C_6 alkyl, $-(CH_2)_tOR^9$, wherein t is an integer from 0 to 6, and the alkyl moiety of the foregoing R^{12} and R^{13} groups is optionally substituted by 1 to 3 substituents independently selected from halo, cyano, trifluoromethyl, $-C(O)R^8$, $-NR^9C(O)R^{10}$, $-C(O)NR^9R^{10}$, $-NR^9R^{10}$, C_1-C_6 alkyl, $-(CH_2)_t(C_6$-C_{10} aryl), $-(CH_2)_t$(5 to 10 membered heterocyclic), $-(CH_2)_tO(CH_2)_qOR^9$, and $-(CH_2)_tOR^9$, wherein t is an integer from 0 to 6 and q is an integer from 2 to 6, or R^{12} and R^{13} may be taken together with the nitrogen to which they are attached to form a C_5-C_9 azabicyclic, aziridinyl, azetidinyl, pyrrolidinyl, piperidinyl, piperazinyl, or morpholinyl ring wherein said C_5-C_9 azabicyclic, aziridinyl, azetidinyl, pyrrolidinyl, piperidinyl, piperazinyl, or morpholinyl ring are optionally substituted by 1 to 5 R^5 substituents, with the proviso R^{12} and R^{13} are not both bonded to the nitrogen directly through an oxygen.

6. The compound of claim 5, wherein R^{11} is $-C(O)NR^{12}R^{13}$, wherein each R^{12} and R^{13} is independently selected from H, C_1-C_6 alkyl, wherein t is an integer from 0 to 6, and the alkyl moiety of the foregoing R^{12} and R^{13} groups is optionally substituted by 1 to 3 substituents independently selected from halo, cyano, trifluoromethyl, $-C(O)R^8$, $-NR^9C(O)R^{10}$, $-C(O)NR^9R^{10}$, $-NR^9R^{10}$, C_1-C_6 alkyl, $-(CH_2)_t(C_6$-C_{10} aryl), $-(CH_2)_t$(5 to 10 membered heterocyclic), $-(CH_2)_tO(CH_2)_qOR^9$, and $-(CH_2)_tOR^9$, wherein t is an integer from 0 to 6 and q is an integer from 2 to 6, or R^{12} and R^{13} may be taken together with the nitrogen to which they are attached to form a C_5-C_9 azabicyclic, aziridinyl, azetidinyl, pyrrolidinyl, piperidinyl, piperazinyl, or morpholinyl ring wherein said C_5-C_9 azabicyclic, aziridinyl, azetidinyl, pyrrolidinyl, piperidinyl, piperazinyl, or morpholinyl ring are optionally substituted by 1 to 5 R^5 substituents, with the proviso R^{12} and R^{13} are not both bonded to the nitrogen directly through an oxygen.

7. The compound of claim 6, wherein R^{11} is $-C(O)NR^{12}R^{13}$ wherein R^{12} and R^{13} taken together with the nitrogen to which they are attached form a C_5-C_9 azabicyclic, aziridinyl, azetidinyl, pyrrolidinyl, piperidinyl, piperazinyl, or morpholinyl ring wherein said C_5-C_9 azabicyclic, aziridinyl, azetidinyl, pyrrolidinyl, piperidinyl, piperazinyl, or morpholinyl ring are optionally substituted by 1 to 5 R^5 substituents.

8. The compound of claim 7, wherein R^{11} is $-C(O)NR^{12}R^{13}$ wherein R^{12} and R^{13} taken together with the nitrogen to which they are attached form a C_5-C_9 azabicyclic, aziridinyl, azetidinyl, or pyrrolidinyl ring wherein said C_5-C_9 azabicyclic, aziridinyl, azetidinyl, or pyrrolidinyl ring are optionally substituted by 1 to 5 R^5 substituents.

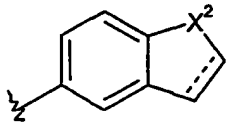
9. The compound of claim 8, wherein R^{11} is $-C(O)NR^{12}R^{13}$ wherein R^{12} and R^{13} taken together with the nitrogen to which they are attached form a C_5-C_9 azabicyclic, azetidinyl or pyrrolidinyl ring wherein said C_5-C_9 azabicyclic, azetidinyl or pyrrolidinyl ring is optionally substituted by 1 to 5 R^5 substituents.

10. The compound of claim 9, wherein R^{11} is $-C(O)NR^{12}R^{13}$ wherein R^{12} and R^{13} taken together with the nitrogen to which they are attached form a C_5-C_9 azabicyclic ring, wherein said C_5-C_9 azabicyclic ring is optionally substituted by 1 to 5 R^5 substituents.

11. The compound of claim 9, wherein R^{11} is $-C(O)NR^{12}R^{13}$ wherein R^{12} and R^{13} taken together with the nitrogen to which they are attached to form an azetidinyl ring, wherein said azetidinyl ring is optionally substituted by 1 to 5 R^5 substituents.

12. The compound of claim 9, wherein R^{11} is $-C(O)NR^{12}R^{13}$ wherein R^{12} and R^{13} taken together with the nitrogen to which they are attached to form a pyrrolidinyl ring, wherein said pyrrolidinyl ring is optionally substituted by 1 to 5 R^5 substituents.

13. Th compound of claim 1, wherein R^2 is a group of the formula



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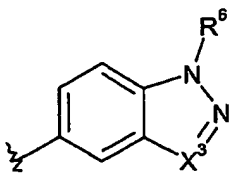

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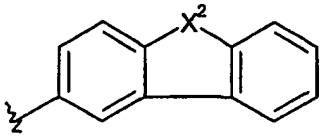

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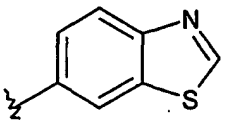

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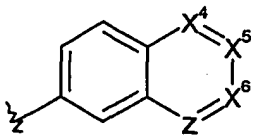
or



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wherein X^2 is -S-, -N(R^6)- or O, and X^3, X^4, X^5, X^6, and Z is N or CH, the dashed line in formula **2** represents an optional double bond, and the above R^2 groups of formulas **2, 4** and **6** are optionally substituted by 1 to 5 R^5 substituents and the R^2 groups of formulas **3** and **5** are optionally substituted by 1 to 3 R^5 substituents.

14. The compound of claim 13, wherein said R^2 group is a group of formula **2** or **6**, wherein said formulas **2** and **6** are optionally substituted by 1 to 5 R^5 substituents.

15. The compound of claim 1, wherein said compound is selected from the group consisting of:

7-(2-Methyl-1H-indol-5-ylamino)-thieno[3,2-b]pyridine-2-carboxylic acid methyl-pyridin-3-ylmethyl-amide;

Azetidin-1-yl-[7-(2-methyl-1H-indol-5-ylamino)-thieno[3,2-b]pyridin-2-yl]-methanone;

[7-(2-Methyl-1H-indol-5-ylamino)-thieno[3,2-b]pyridin-2-yl]-pyrrolidin-1-yl-methanone;

7-(2-Methyl-1H-indol-5-ylamino)-thieno[3,2-b]pyridine-2-carboxylic acid cyclohexyl-methyl-amide;

(2-Methoxymethyl-pyrrolidin-1-yl)-[7-(2-methyl-1H-indol-5-ylamino)-thieno[3,2-b]pyridin-2-yl]-methanone;

7-(2-Methyl-1H-indol-5-ylamino)-thieno[3,2-b]pyridine-2-carboxylic acid methyl-(2-morpholin-4-yl-ethyl)-amid ;

N-{1-[7-(2-Methyl-1H-indol-5-ylamino)-thi no[3,2-b]pyridine-2-carbonyl]-pyrrolidin-3-yl}-acetamide;

N-Ethyl-N-{1-[7-(2-methyl-1H-indol-5-ylamino)-thieno[3,2-b]pyridine-2-carbonyl]-pyrrolidin-3-yl}-acetamide;

(3-Methylamino-pyrrolidin-1-yl)-[7-(2-methyl-1H-indol-5-ylamino)-thieno[3,2-b]pyridin-2-yl]-methanone;

(3-Dimethylamino-pyrrolidin-1-yl)-[7-(2-methyl-1H-indol-5-ylamino)-thieno[3,2-b]pyridin-2-yl]-methanone;

(6-Amino-3-aza-bicyclo[3.1.0]hex-3-yl)-[7-(2-methyl-1H-indol-5-ylamino)-thieno[3,2-b]pyridin-2-yl]-methanone;

(3-Dimethylamino-pyrrolidin-1-yl)-[7-(2-methyl-1H-indol-5-ylamino)-thieno[3,2-b]pyridin-2-yl]-methanone;

(2-Methoxymethyl-pyrrolidin-1-yl)-[7-(2-methyl-1H-indol-5-ylamino)-thieno[3,2-b]pyridin-2-yl]-methanone;

(3-Hydroxy-pyrrolidin-1-yl)-[7-(2-methyl-1H-indol-5-ylamino)-thieno[3,2-b]pyridin-2-yl]-methanone;

(2-Hydroxymethyl-pyrrolidin-1-yl)-[7-(2-methyl-1H-indol-5-ylamino)-thieno[3,2-b]pyridin-2-yl]-methanone;

(3-Methoxy-pyrrolidin-1-yl)-[7-(2-methyl-1H-indol-5-ylamino)-thieno[3,2-b]pyridin-2-yl]-methanone;

(3-Ethoxy-azetidin-1-yl)-[7-(2-methyl-1H-indol-5-ylamino)-thieno[3,2-b]pyridin-2-yl]-methanone;

N-Methyl-N-{1-[7-(2-methyl-1H-indol-5-ylamino)-thieno[3,2-b]pyridine-2-carbonyl]-pyrrolidin-3-yl}-acetamide;

cyclobutanecarboxylic acid {1-[7-(2-methyl-1H-indol-5-ylamino)-thieno[3,2-b]pyridine-2-carbonyl]-pyrrolidin-3-yl}-amide; pharmaceutically acceptable salts of said compounds; solvates of said compounds; and prodrugs of said compounds.

16. The compound of claim 15, wherein said compound is selected from the group consisting of

(2S)-(2-Methoxymethyl-pyrrolidin-1-yl)-[7-(2-methyl-1H-indol-5-ylamino)-thieno[3,2-b]pyridin-2-yl]-methanone;

(+/-)-N-Ethyl-N-{1-[7-(2-methyl-1H-indol-5-ylamino)-thieno[3,2-b]pyridine-2-carbonyl]-pyrrolidin-3-yl}-acetamide;

(3S)-(3-Dimethylamino-pyrrolidin-1-yl)-[7-(2-methyl-1H-indol-5-ylamino)-thieno[3,2-b]pyridin-2-yl]-methanone;

(+/-)-N-Methyl-N-{1-[7-(2-methyl-1H-indol-5-ylamino)-thieno[3,2-b]pyridine-2-carbonyl]-pyrrolidin-3-yl}-acetamide;

(2R)-(2-Methoxymethyl-pyrrolidin-1-yl)-[7-(2-methyl-1H-indol-5-ylamino)-thieno[3,2-b]pyridin-2-yl]-methanone;

(3S)-(3-Hydroxy-pyrrolidin-1-yl)-[7-(2-methyl-1H-indol-5-ylamino)-thieno[3,2-b]pyridin-2-yl]-methanone;

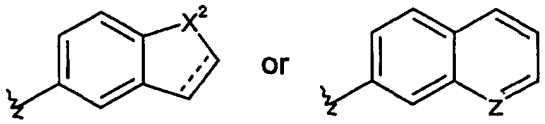
(3R)-(3-Hydroxy-pyrrolidin-1-yl)-[7-(2-methyl-1H-indol-5-ylamino)-thieno[3,2-b]pyridin-2-yl]-methanone;

(+/-)-Cyclobutanecarboxylic acid {1-[7-(2-methyl-1H-indol-5-ylamino)-thieno[3,2-b]pyridine-2-carbonyl]-pyrrolidin-3-yl}-amide;

6-Amino-3-aza-bicyclo[3.1.0]hex-3-yl)-[7-(2-methyl-1H-indol-5-ylamino)-thieno[3,2-b]pyridin-2-yl]-methanone;

(3S)-(3-Methoxy-pyrrolidin-1-yl)-[7-(2-methyl-1H-indol-5-ylamino)-thieno[3,2-b]pyridin-2-yl]-methanone; pharmaceutically acceptable salts of said compounds; solvates of said compounds; and prodrugs of said compounds.

17. A compound of claim 1, wherein X is CH; Y is N; R^1 is H; R^2 is



2 or **6**

X^2 is -N(R^6)-, the dashed line in formula **2** represents an optional double bond, Z is CH or N and the above R^2 group of formulas **2** and **6** are optionally substituted by 1 to 5 R^5.

18. A pharmaceutical composition for the treatment of a hyperproliferative disorder in a mammal which comprises a therapeutically effective amount of a compound of claim 1 and a pharmaceutically acceptable carrier.

19. A method of treating a hyperproliferative disorder in a mammal which comprises administering to said mammal a therapeutically effective amount of a compound of claim 1.

INTERNATIONAL SEARCH REPORT

In ional Application No
PCT/IB 01/00766

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D495/04 A61K31/4365 A61P35/00 A61P13/12

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

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☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
15 November 2001	23/11/2001

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Diederen, J

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INTERNATIONAL SEARCH REPORT

Information on patent family members

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